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SURGICAL APPLICATIONS OF ANTERIOR PERCUTANEOUS LEFT HEART PUNCTURE

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THE measurement of the gradients across the mitral and aortic valves in patients with mitral and aortic stenosis is important in evaluating them as candidates for corrective surgery. Others have reported making these observations by means of left atrial puncture and catheterization of the left ventricle through the left atrial needle[1, 4] or by direct puncture of the left ventricle in patients with aortic valvular disease.[3] In our hands the combination of the suprasternal notch puncture as described by Radner[5] with direct left ventricular puncture has been a satisfactory method of evaluation of these patients and has had advantages over other techniques.

For left atrial puncture the technique of Radner has been used without modification. A flexible needle, 18 cm. long and 0.8 mm. in outside diameter, is passed from the suprasternal notch posterior to the sternum and anterior to the trachea into the left atrium. It usually pierces the arch of the aorta and frequently the pulmonary artery as well on its way into the atrium. If so, pressures are measured in each of these structures on the way in and on withdrawal. If not, it is usually a simple matter to reinsert the needle into either of the great vessels if desired. The patient is supine with the neck extended

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and the head turned to the left. The needle is inserted in the midline and usually reaches the left atrium without difficulty in these patients with valvular heart disease.

Once the needle is in place in the left atrium a second needle, usually a long thin-walled No. 18 with a solid obturator, is inserted into the left ventricle through the anterior chest wall. The chest is entered 1 to 2 cm. medial to the apex impulse in the fifth or sixth left intercostal space and the needle is directed medially, dorsally, and cephalad at an angle of 45 degrees with each of the major planes of the body (Fig. 1). Once the cardiac impulse is felt

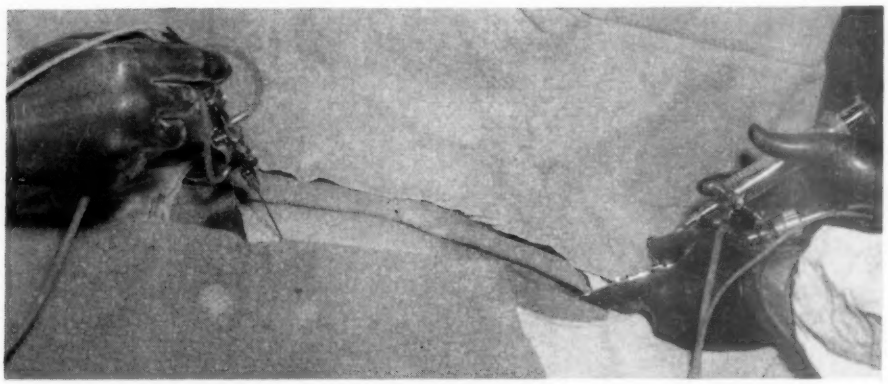

Fig. 1.—Needle in the left atrium is seen at the right, and needle in the left ventricle is seen at the left. To each needle is attached a pressure gauge with appropriate stopcocks and tubing for the flushing of the systems and the measurement of a zero reference plane.

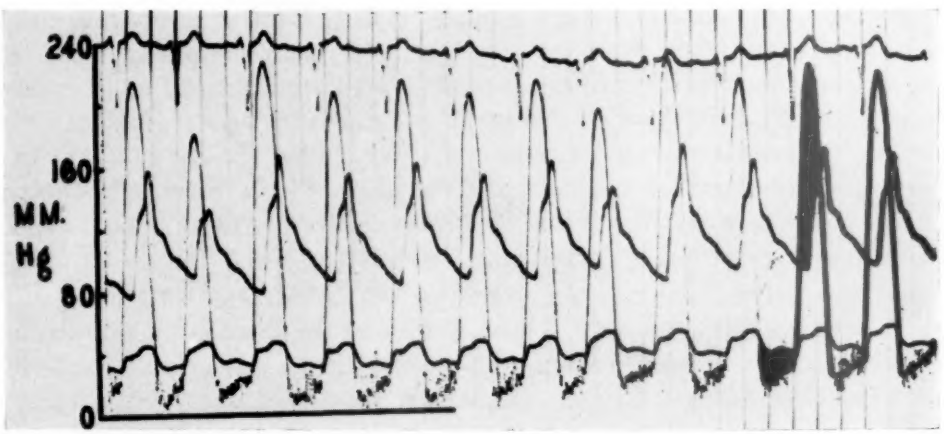

Fig. 2.—Pressure tracings taken simultaneously from the left atrium, left ventricle, and brachial artery. The zero reference and sensitivity are identical for all 3 gauges. The gradients across the mitral and aortic valves are indicated in black in one complex.

with the tip, the needle is advanced quickly. The left ventricle is usually entered directly, or less frequently the right ventricle is pierced on the way into the left ventricle. It is usually easy to tell which ventricle one is in by the color of the blood. In case of doubt the systolic pressure may be compared with the systolic pressure in the systemic and pulmonary arteries, or a sample

may be withdrawn for gas analysis. If one simultaneously measures the pressure in a systemic artery, one has simultaneously the gradients across both the mitral and aortic valves (Fig. 2). Alternatively one may measure the gradient first across the mitral valve and then withdraw the suprasternal needle to the aorta and measure pressure across the aortic valve.

The pressure gradients across the valves are important data but are more significant if simultaneous measurements of blood flow are made. The techniques just described are well adapted for combination with right heart catheterization and measurement of cardiac output by the direct Fick procedure since the patient is supine throughout the test (Fig. 3). It is also possible to measure blood flow by a dye dilution technique. When the patient is anesthetized with a volatile anesthetic, as many are in our series, the dye technique is desirable. When only local anesthetic is used, the direct Fick can be applied.

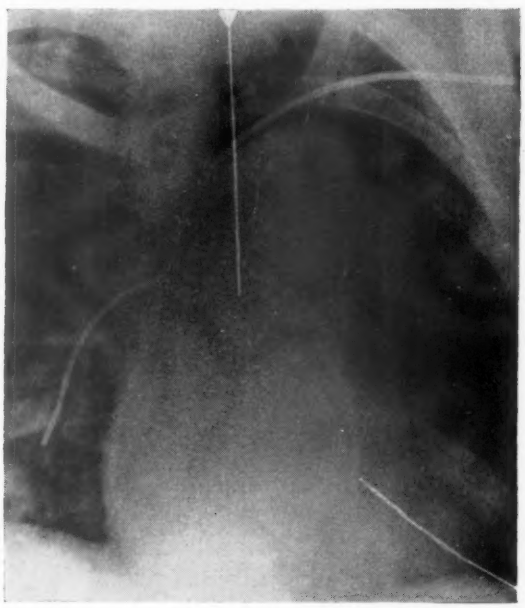

Fig. 3.—Roentgenogram of the chest showing the ventricular and suprasternal needles in place and also a catheter in the pulmonary artery for the measurement of blood flow. Needles retouched.

The precautions to be observed in making these observations are those to be used in any similar procedure. Radner believes that the safety of the suprasternal puncture with piercing of both main arterial trunks depends upon the fine caliber of the needle used. He advises against using a needle larger than 0.8 mm. in outside diameter, and we have followed his advice. This restriction prevents using this needle for sampling, injections, or the insertion of a catheter. It also necessitates high quality pressure pick-ups with suitable membrane and frequency characteristics and leak-tight stopcocks and connections. We use the special Y connector described by Radner. Care is taken to prevent the introduction of bubbles into the systemic circulation. Continuous electrocardiographic monitoring is routine.

The complications have been gratifyingly few. In the 18 patients whose pericardiums have been opened immediately following the procedure, no bleeding point was visualized at the time of surgery. Usually 75 to 100 ml. of bloody pericardial fluid is found. In only one case was this amount exceeded, about 150 ml. being present. Two patients have had hemoptysis following the procedure. In one this necessitated postponing the scheduled thoracotomy, while in the other the bronchi were cleared of blood by bronchoscopy. Of the 5 patients who have not undergone thoracotomy immediately following the procedure all have had some chest pain of minor degree for 1 to 4 days. Two have had low-grade fever for the same period of time. Premature ventricular beats have been noted in all patients at the time of piercing the epicardium with the left ventricular needle, but these always stop spontaneously when the tip is advanced further.

The study of patients about whom some doubt is entertained clinically may be rewarding in terms of decisive information. One such patient was operated upon for mitral stenosis in August, 1954, at the age of 51 because of increasing dyspnea and orthopnea progressing over the previous year. She had also noted chest pain for 3 years. Physical examination showed atrial fibrillation and typical signs of mitral stenosis. She also had pulmonary emphysema. The x-ray and electrocardiographic findings were confirmatory. At surgery a leathery funnel type of mitral stenosis was found which was not successfully sectioned. The opening was dilated somewhat but on the whole the procedure was considered unsatisfactory. She was only moderately improved. After 1½ years progressive return of symptoms was noted along with anginal pain. Despite a grade II aortic systolic murmur the diagnosis of aortic stenosis was not considered established, and she was scheduled for reoperation for mitral stenosis. The measurement of significant gradients across both the mitral and aortic valves just prior to thoracotomy established clearly the presence of stenosis of both valves and aided in the planning of surgery.

The combination of the suprasternal puncture with direct anterior puncture of the left ventricle has been less hazardous in our hands than the right posterior approach to the left atrium with catheterization of the left ventricle through the left atrial needle. The percentage of successful measurements of the left ventricular pressure has also been higher. No fluoroscopic guidance is necessary, which simplifies the procedure. The supine position of the patient facilities combination with either direct Fick or dye dilution techniques of measuring blood flow. In straightforward cases in which the patients are scheduled for surgery on clinical grounds it is a convenient confirmatory check just before thoracotomy. Measurement through a wide-bore rigid needle with a high-frequency manometer gives a more accurate record of left ventricular pressure than is usually obtained otherwise. In Fig. 2, the vibrations of the diastolic murmur can be seen in the ventricular pressure tracing.

The measurement of pressure gradients across the mitral and aortic valves may be made with the heart exposed at the time of thoracotomy, before and after any corrective procedure for stenosis. The findings before the corrective

manipulation agree reasonably well with the findings in the closed chest in our series, as has been noted by others.[2] Either may serve as a satisfactory basis for comparison with the measurements after manipulation. While in some cases the patient's condition is so changed that such a comparison is of no value, it is frequently of help in the decision as to whether enough opening of the valve has been obtained.

SUMMARY

The suprasternal notch approach for left atrial puncture may be easily combined with direct anterior puncture of the left ventricle to permit measurement of pressure gradients across the mitral and aortic valves. These measurements may be combined with cardiac output determinations. The advantages of this procedure over left heart catheterization include the supine position, relative freedom from untoward sequellae, and lack of need for fluoroscopic control.

REFERENCES

1. Björk, V. O.: Direct Pressure Measurement in the Left Atrium, the Left Ventricle and the Aorta, Acta chir. scandinav. **107**: 466, 1954.
2. Brock, Sir Russell: Surgical Treatment of Aortic Stenosis, Brit. M. J. **1**: 1019, 1957.
3. Brock, Sir Russell, Milstein, B. B., and Ross, D. N.: Percutaneous Left Ventricular Puncture in the Assessment of Aortic Stenosis, Thorax **11**: 163, 1956.
4. Fisher, Don L.: The Use of Pressure Recordings Obtained at Transthoracic Left Heart Catheterization in the Diagnosis of Valvular Heart Disease, J. Thoracic Surg. **30**: 379, 1955.
5. Radner, Stig: Extended Suprasternal Puncture Technique, Acta med. scandinav. **151**: 223, 1955.

Discussion

DR. RAYMOND O. HEIMBECKER (Toronto, Canada).—We have performed left heart catheterization on 90 selected problem cases, using a modification of the Björk method, in which a side arm is fastened to the needle. It is passed through the posterior chest wall and into the left atrium under local anesthesia. With the side arm and a loose-fitting catheter, a recording is obtained of the ventricle through the catheter and of the atrium around the catheter. It is of interest that in one-third of our cases combined mitral and aortic valve lesions were either present or at least suspected, which makes this combined study of aortic and mitral disease of great value. Dye curves recorded cardiac output and thus valve area. They are being further developed to estimate the amount of regurgitation present across the mitral valve. The mortality rate has been zero, and entry into the heart has been 94 per cent successful. Our findings have been confirmed at operation or autopsy in two-thirds of the cases, with only 2 minor errors in interpretation of tracings. Many patients have thus avoided a useless thoracotomy, while many more, previously considered inoperable, have been found to have correctable lesions and so have benefited from operation.

(Slide.) Angiography through the left atrium seems to be a very feasible procedure. Here is the needle in the left atrium, through which 50 per cent Diodrast has been injected. The aortic and mitral valve cusps are outlined. This is apparently a safe means of delineating the coronary arteries. We are pursuing this further to see what value it has in suspected coronary artery disease.

DR. LEWIS H. BOSHER, JR. (Richmond, Va.).—I would like to report a very unfortunate experience with left atrial puncture. This was in the case of a young girl, 13 years of age, in whom puncture was made by the posterior route. Two attempts to enter the left atrium were unsuccessful. No blood was obtained, although we felt certain the heart had been punctured. The needle was withdrawn, a different position was selected, and a high-pressure chamber was entered. Two minutes after withdrawing the needle, the

patient experienced severe pain in the abdomen which at first was attributed to hemopericardium, but subsequently it became apparent that it was due to saddle embolus. Embolectomy was performed. The patient experienced another embolus to the cerebrum during operation and died approximately 48 hours later. Post-mortem examination showed a large thrombus posteriorly in the left atrium from which emboli very obviously had come. This was all the more remarkable in that the patient was a young girl with normal sinus rhythm who had a pure mitral insufficiency.

We have also been disturbed by one other feature. After a perfectly uncomplicated puncture in a patient upon whom we operated 3 months after atrial puncture, we encountered a very disturbing deposition of fibrin over the surface of the heart which seemed almost to be constricting. It was not possible to remove all of this fibrin coating from the supra-aortic approach that we had selected.

I think we must recognize various complications which accompany this diagnostic measure.

DR. DAVID D. GREENE (Closing).—As I pointed out, the left atrial needle from the anterior approach is not suitable for injection of contrast media. The left ventricular needle, however, is a No. 18 thin-walled needle and would be suitable for injection as has been done recently in Sweden. I am interested in Dr. Bosher's difficulties with these patients. I do not see how anyone could have avoided the embolus by any technique. I think one advantage of the suprasternal approach is that one generally does not cross free pericardium and therefore perhaps one would not get pericardial blood and fibrin by this method. We attribute blood found to ventricular puncture and not atrial puncture.

INDUCED CARDIAC ARREST (CARDIOPLEGIA) IN OPEN HEART SURGICAL PROCEDURES

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DURING the past year, the procedure of induced cardiac arrest as an adjunct during operations which require visualization of the interior of the heart has received increasing acceptance by cardiac surgeons. The advantages of a quiet heart and one which is freer of blood than with caval occlusion alone are obvious. We began a study of methods of producing cardioplegia in the fall of 1952.[4] It was found that a solution of potassium chloride injected into the left ventricle produced profound arrest, and, with the brain protected by hypothermia, various operations on the cardiac septa and valves in experimental animals were carried out. Since we had no pump-oxygenator at that time, resuscitation had to be obtained by manual systole. This method of reviving the heart was undoubtedly largely responsible for the high incidence of ventricular fibrillation encountered during the recovery phase. We then investigated the value of the drug acetylcholine as a cardioplegic agent and found that ventricular fibrillation was less frequently encountered during cardiac massage. It was also noted that the ideal way to resuscitate the heart was to perfuse the coronary arteries with ogygenated blood.[7] When a pump-oxygenator of the bubble type became available to us early in 1956, we began to use it in open heart procedures, and the heart has been arrested with acetylcholine during the cardiotomy in all of the 88 cases reported here.

METHOD

The cannulations for carrying out the cardiac by-pass with the pump-oxygenator of the bubble type have been essentially that described by Lillehei, DeWall, and their associates at the University of Minnesota.[2, 3] The only variation in the caval cannulation was in the one case in which transposition of the great vessels was corrected by a plastic procedure on the interatrial septum. In this instance, the inferior cava was cannulated through a saphenous vein and the superior cava was entered directly through an extrapericardial opening. The left subclavian artery is ideal for the introduction of the return cannula from the pump-oxygenator. In several early cases of atrioventricularis communis, we utilized a right unilateral thoracotomy and hence had to use the right subclavian artery. We found the cannulation of the

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right subclavian artery difficult, and we now use the bilateral thoracotomy of the transverse type so that the left subclavian artery is available on all procedures in which cardiac by-pass is planned.

When the cannulations are complete, the motor of the pump-oxygenator is started and the caval snares are tightened. After about 2 minutes of a test run and when it is certain that inflow and outflow circuits are satisfactory, the heart is stopped. A figure-of-eight suture of 5-0 silk is placed in a convenient place on the ascending aorta near the heart (Fig. 1). A nonerushing clamp is then placed across both the aorta and pulmonary artery. Clamping both great vessels makes it unnecessary to carry out the dissection necessary to separate them. A calculated dose of acetylcholine (10 mg. per kilogram of body weight, diluted in 15 to 20 c.c. of saline solution) is injected through a large bore needle into the aorta through the previously placed suture. The entire dose of cardioplegic drug is given even though the heart ceases to beat during the injection. The incision is then made into the appropriate cardiac chamber or great vessel. The most common incision, as for closure of interventricular septal defects, is through the right ventricle. The heart may respond to mechanical stimulation with single contractions, but this is not troublesome and usually there is no cardiac activity during the actual suturing of the defect. Rarely, it may be necessary to give a second injection of acetylcholine because of resumption of spontaneous cardiac activity.

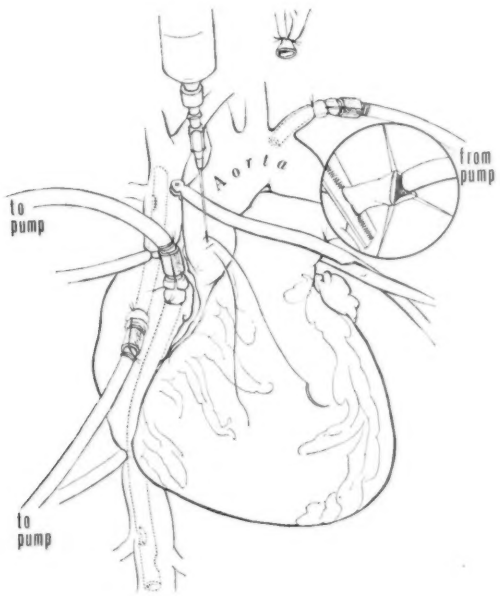

Fig. 1.—Diagram of cannulations for cardiac by-pass with the pump-oxygenator and method of producing cardiac arrest by the injection of acetylcholine into the clamped aorta.

After the intracardiac part of the operation is done, the heart is permitted to resume its beat during the closure of the ventricular or atrial incision. Resuscitation is accomplished simply by removing the clamp from the great vessels, which permits the perfusion of the coronary arteries with oxygenated

blood and the drug is washed out. The first coronary sinus blood containing the drug is removed from the ventricle or auricle by aspiration. The incision into the heart chamber is not completed until the heart is beating actively with the result that all air is expelled. There has been no instance of air embolism to the coronary or cerebral arteries in the 88 operations herein reported. A typical electrocardiogram taken before, during, and after induced arrest is shown in Fig. 2.

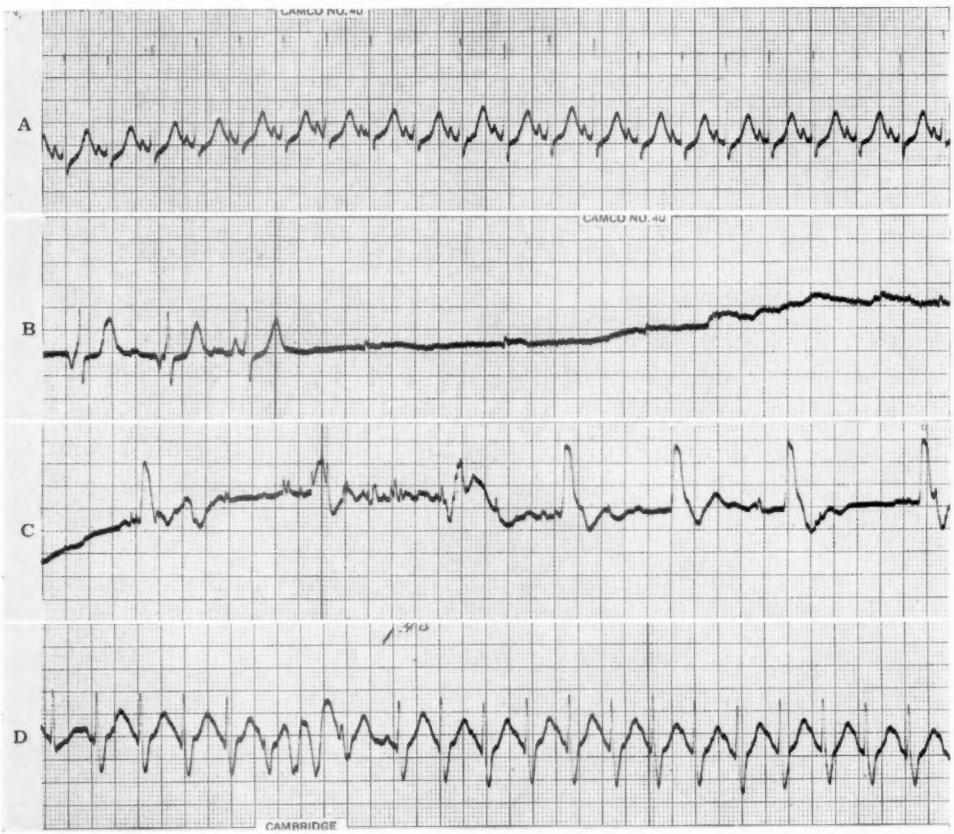

Fig. 2.—Electrocardiograms taken during operation for closure of interventricular septal defect in a 4-year-old child. *A*, Normal tracing. *B*, Sustained asystole following injection of acetylcholine. *C*, Tracing taken 2 minutes following removal of aortic clamp, showing resuscitation of heart. *D*, Tracing taken during closure of thoracotomy incision, with return to normal pattern.

CLINICAL RESULTS

Induced cardiac arrest has been used as an adjunct in 58 operations in 57 patients for the repair of interventricular septal defects. The discrepancy between the number of operations and the number of patients is due to the fact that an early patient in the series had a second operation because of recurrence of the defect. The technical aspects of the closure in the first operation were not satisfactory because of an excess of intracardiac blood due to an overlooked left superior vena cava.

In the majority of the operations for the repair of interventricular septal defects, the suturing was carried out with remarkable facility because of the

presence of a quiet dry heart (Fig. 3). Details of the technical procedures employed have been reported elsewhere.[3] In the last 45 cases, a uniform technique of closure has been adopted. Interrupted sutures are passed through the margins of the defect by means of sutures with needles attached to each end (Fig. 4). An attempt is made to cause the sutures to encompass only white fibrous tissue, such as is usually encountered on the left ventricular side of the septum. Where this fibrous tissue has been available for the repair, atrioventricular block has never occurred. Ventricular fibrillation was encountered 3 times in the resuscitative phase of the operations. One of these patients had fibrillation twice before the pump-oxygenator was attached. Sinus rhythm was established promptly in each of the 3 cases with one countershock. In 5 of the patients, persistent atrioventricular block seemed to be the chief factor in the fatal outcome, giving an incidence of 8.7 per cent for the complication. It is unlikely that this incidence is higher than that obtained by surgeons who close ventricular septal defects without stopping the heart. Therefore the complication cannot be considered to be one related to the cardioplegia per se.

The mortality rates in operations for the closure of ventricular septal defects in the various age groups are shown in Table I. The high total mortality rate of 33 per cent is due to the fact that it takes into account 9 small infants who were operated upon because they had ceased to grow and appeared to be near death. In contrast, in the group of children over the age of 3 years, the mortality rate was less than 5 per cent.

TABLE I. MORTALITY RATES IN CLOSURE OF VENTRICULAR SEPTAL DEFECTS

AGE	NUMBER OF CASES	DEATHS	MORTALITY RATE (PER CENT)
All cases	58	19	33.0
Under 1 year	14	9	65.0
Over 1 year	44	11	25.0
Over 2 years	29	5	17.0
Over 3 years (pumped 50 c.c./kilo/min.)	21	1	4.8

By far the most common type of cardiac lesion for which an operation with induced cardiac arrest was used was isolated ventricular septal defect, which accounted for 58 operations. To this can be added a miscellaneous group of 30 operations. Details of the procedures in some of the latter group have been previously reported.[2] There have been 4 cases of atrioventricularis communis. In each case, the cleft in the mitral valve has been repaired and the large atrial defect closed. All 4 of these children survived the immediate postoperative period, but 2 died later. In one of these, the repair seemed to be satisfactory but there was a single coronary artery. The other had a persistent atrioventricular block and expired 3 months after the operation; the sutures in the valve area had cut through, producing a recurrence of the interatrial septal defect. This experience suggested that the use of an Ivalon prosthesis set in place with circumferential sutures might be advisable.

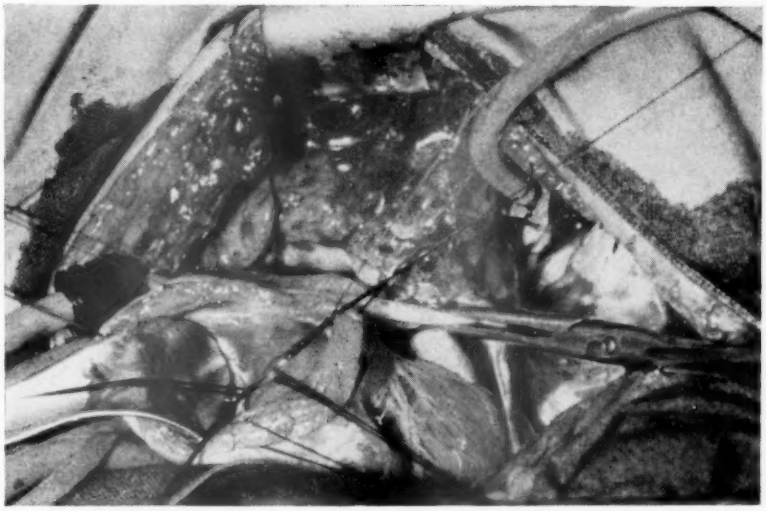

Fig. 3.—Photograph of operation during closure of ventricular septal defect. Note the clamp on the aorta and pulmonary artery, the retractor in the right ventricular incision, and the 3 sutures placed through the margins of the defect. Note particularly the completely dry field.

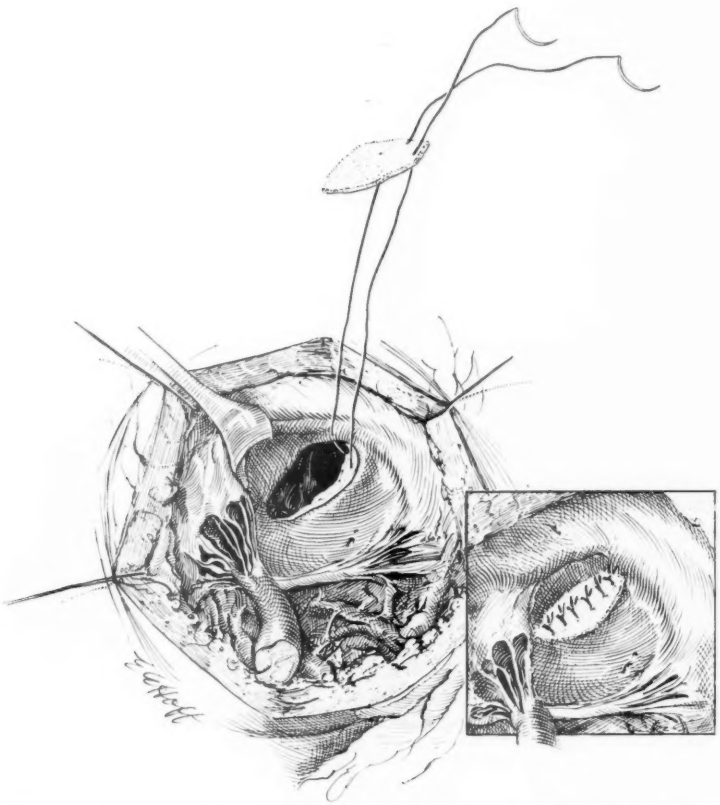

Fig. 4.—Details of typical closure of interventricular septal defect. The sutures are passed through and tied over a pledget of compressed Ivalon sponge.

We have carried out direct operations on only 4 cases of tetralogy of Fallot. Three of these were desperate cases of shunt failure. There has not been a survival in this group. Three children died with persistent atrioventricular block, and another died of undetermined causes 20 hours after an apparently successful operation. Efforts to relieve valvular insufficiency were unsuccessful in 2 cases of aortic valvular disease and one case each of tricuspid and mitral insufficiency. Three infants with single ventricles died following exploration. Three attempts to correct complete transposition of the great vessels were unsuccessful. The most promising operation involved a plastic procedure on the interatrial septum. The color of the infant was remarkably improved for a few hours, but death resulted from persistent heart block.

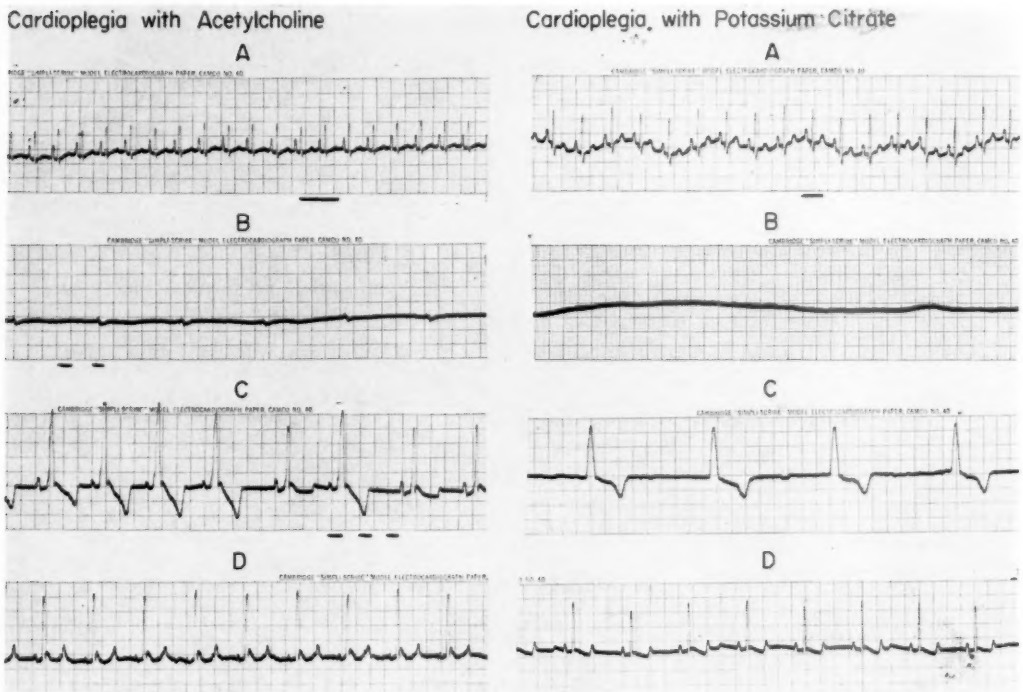

Fig. 5.—Comparison of electrocardiographic tracings in animals with cardioplegia produced with acetylcholine and with potassium citrate. *A*, Normal tracing. *B*, During arrest. *C*, Three minutes after removal of aortic clamp and beginning of coronary perfusion with oxygenated blood. *D*, Tracings taken after full recovery of the hearts. Note that atrial activity persisted in the heart arrested with acetylcholine and that recovery was more rapid.

Fatalities occurred after 2 operations for complete pulmonary atresia, after correction of very complicated interatrial septal defects with unusual venous anomalies and after the excision of a huge aneurysm of the ascending aorta which was eroding the anterior chest wall. Successful operations were carried out in one of 2 cases of congenital aortic stenosis, one instance of fistula between the left ventricle and right atrium, infundibular stenosis, and myxoma of the right atrium associated with an atrial septal defect. Details of the latter case will be published separately. Suffice it to say that with cardiac bypass and right atriotomy the huge tumor, which arose from the margin of the

atrial septal defect and prolapsed through the tricuspid valve as well as the defect, was easily delivered and excised, after which the defect in the septum was closed.

ACETYLCHOLINE VERSUS POTASSIUM CITRATE AS THE CARDIOPLEGIC AGENT

After we had adopted the drug acetylcholine as the agent for producing cardiac arrest, our attention was drawn to the experimental work of Melrose[5] of London. He recommended that the heart be stopped by the intracoronary injection of heparinized blood containing potassium citrate. This method has been used clinically by Effler and his associates.[1] Because we had discontinued the use of potassium chloride for reasons outlined above, we were not inclined to try the Melrose method clinically. We performed a few experiments in the laboratory to compare the 2 methods.[6] The periods of resuscitation were slightly longer with the potassium citrate and there was one instance of intractable fibrillation, a complication which did not occur when acetylcholine was used.

Fig. 5 shows a comparison of the electrocardiographic tracings made at comparable phases during induced arrest with acetylcholine and potassium citrate. It will be noted that some activity (probably atrial contractions) persisted during the acetylcholine arrest; this activity was not present with the potassium citrate. Apparently, the latter heart was more completely arrested. Perhaps this is a disadvantage when restoration of the heartbeat is so essential.

SUMMARY

The agent acetylcholine has been used to produce cardioplegia (induced cardiac arrest) in 88 human cases as an adjunct during intracardiac surgical procedures. Fifty-eight of the operations have been for the closure of interventricular septal defects, and 30 have been for the correction of a great variety of congenital and acquired lesions. The method has appeared to be safe and valuable for use in these open heart operations.

REFERENCES

1. Effler, D. B., Groves, L. K., Sones, F. M., and Kolff, W. J.: Elective Cardiac Arrest in Open-Heart Surgery: Report of Three Cases, Cleveland Clin. Quart. **23**: 105, 1956.
2. Lam, C. R., Gahagan, Thomas, Sergeant, C. K., and Green, Edward: Clinical Experiences With Induced Cardiac Arrest During Intracardiac Surgical Procedures, Ann. Surg. **146**: 439, 1957.
3. Lam, C. R., Gahagan, Thomas, Sergeant, C. K., and Green, Edward: Experiences in the Use of Cardioplegia (Induced Cardiac Arrest) in the Repair of Interventricular Septal Defects, J. Thoracic Surg. **34**: 509, 1957.
4. Lam, C. R., Gahagan, Thomas, and Lepore, Alfredo: Induced Cardiac Arrest for Intracardiac Surgical Procedures, J. Thoracic Surg. **30**: 620, 1955.
5. Melrose, D. G., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective Cardiac Arrest, Lancet **2**: 21, 1955.
6. Mota, Carlos, Gahagan, Thomas, and Lam, C. R.: A Comparison of Acetylcholine and Potassium Citrate as Cardioplegic Agents, Proc. Mich. Acad. Sc., Arts & Letters, 1957. In press.
7. Sergeant, C. K., Gahagan, Thomas, and Lam, C. R.: Further Studies in Induced Cardiac Arrest Using the Agent Acetylcholine, Surg. Forum, Am. Coll. Surgeons **7**: 254, 1956.

(For discussion see page 21)

A COMPARISON OF THE RESULTS OF TOTAL BODY PERFUSION IN DOGS DURING POTASSIUM CITRATE CARDIAC ARREST, SINUS RHYTHM, AND INDUCED VENTRICULAR FIBRILLATION

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(From the Children's Hospital Research Foundation and the Departments of Pediatrics and Surgery, College of Medicine, University of Cincinnati, and the Fels Institute for Research in Human Development, Antioch College)

THE development of methods for total body perfusion has advanced to the stage where intra- and extracardiac lesions can be treated successfully under direct vision. Our clinical experience soon demonstrated that in many instances the intracardiac procedure is more difficult if the coronary circulation is maintained and the heart continues to beat during the perfusion. These 2 factors could be avoided if cardiac arrest were temporarily induced with an agent that had a known and reversible effect. This report compares the results of total body perfusion in 40 dogs during potassium citrate cardiac arrest, sinus rhythm, and induced ventricular fibrillation.

METHOD

Animals weighing between 5 and 26 kilograms were anesthetized with intravenous sodium pentobarbital (25 mg. per kilogram) and were ventilated with 100 per cent oxygen through a closed endotracheal system. The pleura was entered through the right fourth intercostal space. The animals were given 1.5 mg. of heparin per kilogram of body weight intravenously prior to cannulation for cardiopulmonary by-pass. Venous blood for oxygenation and removal of an adequate amount of carbon dioxide was obtained from the venae cavae by cannulas inserted through the right atrial appendage into the inferior vena cava and from the azygos vein into the superior vena cava. Arterial blood was returned from the Clark heart-lung apparatus through the left femoral artery. The principles of this machine have been described elsewhere.[2, 4, 8] In summary, blood is oxygenated by bubbles of oxygen dispersed in the blood. Excess gas is coalesced on a polymethylsiloxane surface and eliminated. Blood is pumped by an alternating suction and pressure controlled by 2 electrodes which actuate 2 solenoid valves. The electropolished stainless steel parts of the apparatus which are in contact with blood are treated by boiling in Monocote (Armour).

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The venous and arterial cannulas which are of thin-walled electropolished stainless steel were similarly treated. The glass parts of the apparatus were vapor coated with Drifilm (General Electric). Tygon tubing was used throughout. The complete unit can be autoclaved. The machine was primed with freshly collected heparinized blood (25 mg. per liter).

When an adequate flow rate was obtained from the apparatus, temporary ligatures around the superior and inferior venae cavae were tightened at their point of entry into the right atrium. In 18 animals the heart was arrested by the injection of the Melrose[11] potassium citrate blood mixture into the ascending aorta after it had been cross-clamped. In 22 animals the coronary flow was maintained throughout perfusion. In the latter group the heart was allowed to remain in sinus rhythm in 8 instances and in 14 experiments ventricular fibrillation was induced electrically. A right auriculotomy or ventriculotomy was performed in 34 of the 40 animals. The coronary and bronchial venous blood was gently aspirated from the cardiotomy and left atrium and returned to the machine. In the experiments where the heart was arrested with potassium citrate, the aorta was released after completion of the cardiotomy and 100 to 200 c.c. of blood was aspirated from the right heart and discarded. When ventricular fibrillation was induced, this was reversed by electrical countershock.[7] After completion of the period of cardiopulmonary by-pass, the flow rate from the machine was slowly reduced. Both pleural spaces were drained by indwelling catheters. After completion of the perfusion, protamine sulfate was infused intravenously over a period of 1 to 2 hours. The dose of protamine sulfate depended upon a protamine titration on a sample of the recipient's blood after completion of the perfusion. The amount of protamine given was based upon the calculated dose which would restore the clotting time to less than 6 to 8 minutes. Protamine titrations were also performed on the donor blood before the apparatus was primed to confirm that the donor blood has been adequately heparinized.

RESULTS

Each parameter will be divided into the following groups: (1) those in which the heart remained in sinus rhythm or in which ventricular fibrillation was induced electrically during total perfusion (22 experiments) and (2) those in which the heart was arrested with potassium citrate during cardiopulmonary by-pass (18 experiments).

Survival Rate (Table I).—In the 22 experiments in which cardioplegia was not used, 20 animals (90 per cent) were long-term survivors. The survivors were sacrificed between 2 and 24 weeks after perfusion. They behaved as normal animals and at autopsy did not reveal any abnormalities. The 2 animals of this group that did not survive died 34 to 36 hours after surgery and it is believed that the mechanism of their death was due to low flow rates during perfusion.

TABLE I. SURVIVAL RATE

SINUS RHYTHM		VENTRICULAR FIBRILLATION		POTASSIUM CITRATE ARREST	
SURVIVED	DIED	SURVIVED	DIED	SURVIVED	DIED
8	0	12	2	9	9

In the 18 experiments in which potassium citrate cardiac arrest was used, the mortality rate was 50 per cent. The 9 surviving animals behaved normally after surgery and 8 were sacrificed between 3 and 24 weeks after perfusion. At autopsy no unusual macroscopic abnormalities were detected. One animal is at present surviving 30 weeks after perfusion. In the 9 survivors, 3 animals had ventricular fibrillation during release of the cardioplegia.

Of the 9 animals that did not survive, death occurred within one hour after completion of the cardiotomy in 7 instances. In one of these animals normal cardiac function returned after potassium citrate release but the mean arterial pressure remained below 50 mm. Hg and irreversible ventricular fibrillation occurred one hour later. In the remaining 6 animals the following sequence of events occurred. After completion of the cardiotomy, the clamp across the ascending aorta was removed and 100 to 200 c.c. of blood was aspirated from the right ventricle. An apparently normal contraction returned to both atria and the right ventricle but the left ventricle assumed an irreversible state of tonic contraction. Within a few minutes the right ventricle and atrium dilated and ventricular fibrillation was noted to involve both ventricles. The fibrillatory movement in the right ventricle was coarse whereas the left ventricle remained in tonic contraction but in addition exhibited a fine fibrillatory movement. This state was irreversible and unaffected by the reinjection of potassium citrate into the coronary circulation.

Two animals that did not survive potassium citrate cardiac arrest died 12 to 18 hours after perfusion. Both of these animals had systemic pressures below 60 mm. Hg after perfusion and were slow to respond to stimulants. At autopsy the cause of death was due to diffuse hemorrhagic collapse of the lungs.

Duration of Perfusion (Table II).—

TABLE II. DURATION OF PERFUSION IN MINUTES

SINUS RHYTHM			VENTRICULAR FIBRILLATION			POTASSIUM CITRATE ARREST		
P.P.	T.	P.T.	P.P.	T.	P.T.	P.P.	T.	P.T.
11-31 (16)	30-42 (35)	2-11 (6)	17-30 (25)	23-57 (47)	5-20 (10)	9-30 (20)	29-67 (49)	11-47 (20)

P.P. = partial perfusion.
T. = total perfusion.
P.T. = partial perfusion after total.
The figures in parentheses indicate the mean time.

Sinus rhythm series: In this group the period of total perfusion is designated as that time between the beginning of the cardiotomy and the release of the temporary ligatures around the venae cavae. This varied between 30 and 42 minutes with a mean of 35 minutes. This period was preceded by a period of partial perfusion varying from 11 to 31 minutes with a mean of 16 minutes. The time of partial perfusion after completion of total perfusion varied from 2 to 11 minutes with a mean of 6 minutes.

Ventricular fibrillation series: The period of total perfusion was timed between the induction of ventricular fibrillation and electrical defibrillation. This varied between 23 and 57 minutes with a mean of 47 minutes. The period

of partial perfusion preceding ventricular fibrillation varied from 17 to 30 minutes with an average of 25 minutes. The time of partial perfusion after defibrillation varied from 5 to 20 minutes, with a mean of 10 minutes.

Potassium citrate series: The period of total perfusion was timed between the onset of cardiac arrest and the release of the temporary ligatures around the venae cavae. This varied from 29 to 67 minutes with an average of 49 minutes. This was preceded by a period of partial perfusion varying from 9 to 30 minutes with an average of 20 minutes. In the animals that survived, the period of partial perfusion after cardioplegia varied from 11 to 47 minutes with an average of 20 minutes.

Blood Temperature.—During extracorporeal circulation large volumes of blood are exposed to room temperature. Precautions were taken to deliver arterial blood to the animals at a temperature of 35.5° to 37.5° C. This was accomplished by thermostatically controlled circulating water at 50° C. through a double-walled silver tube placed in the venous inlet of the apparatus. The temperature of the blood returning to the animals was comparable in the above groups.

Blood Pressure.—Mean arterial blood pressures were continuously recorded from the right femoral artery (Table III). Blood transfusions were given according to estimated and measured blood loss.

TABLE III. MEAN ARTERIAL BLOOD PRESSURE IN MM. HG

	SINUS RHYTHM	VENTRICULAR FIBRILLATION	POTASSIUM CITRATE ARREST
Prior to cannulation	60-150 (100)	57-130 (96)	80-154 (121)
Partial perfusion	50-150 (100)	31-150 (80)	71-157 (104)
Total perfusion	45-100 (71)	26- 90 (51)	57-136 (92)
After cardiotomy	80-130 (105)	56-150 (80)	40-133 (63)

The figures in parentheses indicate average mean pressures.

Sinus rhythm series: Prior to cannulation of the venae cavae the mean systemic blood pressure varied from 60 to 150 mm. Hg (average 100 mm. Hg). During partial perfusion the mean pressure varied from 50 to 150 mm. Hg (average 100 mm. Hg). During total perfusion the mean pressure varied from 45 to 100 mm. Hg (average 71 mm. Hg). After completion of the cardiotomy and excannulation the mean pressure varied from 80 to 130 mm. Hg (average 105 mm. Hg).

Ventricular fibrillation series: Prior to cannulation of the systemic veins the mean arterial pressure varied from 57 to 130 mm. Hg (average 96 mm. Hg). During partial perfusion the mean pressure varied from 31 to 150 mm. Hg (average 80 mm. Hg). During total perfusion the mean pressure varied from 26 to 90 mm. Hg (average 51 mm. Hg). After defibrillation and excannulation the mean pressure varied between 56 and 150 mm. Hg (average 80 mm. Hg). It is noteworthy that the 2 animals of this series that did not survive maintained the lowest mean arterial pressure during and after total perfusion.

Potassium citrate series: Prior to cannulation of the venae cavae the mean arterial pressure varied between 80 and 154 mm. Hg (average 121 mm. Hg). During partial perfusion the mean pressure varied from 71 to 157 mm. Hg (average 104 mm. Hg). During total perfusion the mean pressure varied from 57 to 136 mm. Hg (average 92 mm. Hg). In the surviving animals the mean pressure for 4 to 6 hours after perfusion varied from 40 to 133 mm. Hg (average 63 mm. Hg).

Arterial and Venous pO_2.—Polarographic measurements of the partial pressure of oxygen in the arterial blood were continuously recorded in all experiments. The oxygen electrode has been previously described by Clark.[1, 3, 5] In all instances the partial pressure of oxygen was kept constantly between 600 and 650 mm. Hg. In 17 experiments the partial pressure of oxygen in the venous blood was continuously recorded from a cathode placed in the line carrying blood from the superior vena cava. The venous pO_2 varied from 30 to 45 mm. Hg which was equivalent to a venous saturation of 59 to 79 per cent.

Arterial pH.—The pH of the arterial blood from the apparatus was continuously recorded in 36 experiments. The details of the method will be described elsewhere. The results are shown in Table IV. The arterial pH and pO_2 were controlled by using a combination of small (±20 micron) and large (±200 micron) bubbles of oxygen for oxygenation. Adequate amounts of carbon dioxide are removed by the large bubbles and efficient oxygenation is achieved by the large surface area produced by small bubbles.[1] In 8 experiments measurement of blood lactic acid and bicarbonate indicated that metabolic acidosis did not occur.

TABLE IV. ARTERIAL PH

	SINUS RHYTHM	VENTRICULAR FIBRILLATION	POTASSIUM CITRATE ARREST
Partial perfusion	7.45-7.50	7.42-7.52	7.43-7.52
Total perfusion	7.40-7.45	7.43-7.48	7.40-7.48
After total perfusion	7.40-7.50	7.40-7.53	7.40-7.52

Plasma Hemoglobin.—The plasma hemoglobin was measured as an index of destruction of the red blood corpuscles during extracorporeal circulation. The measurements were determined colorimetrically on the donor blood and from samples taken from the apparatus after completion of perfusion. The difference between these 2 figures is attributed to hemolysis during extracorporeal circulation. These differences are indicated in Table V. The major cause of hemolysis was due to turbulence produced by aspiration of blood from the open heart.

TABLE V. INCREASE IN PLASMA HEMOGLOBIN (MG. PER CENT) DURING PERFUSION

SINUS RHYTHM	VENTRICULAR FIBRILLATION	POTASSIUM CITRATE ARREST
63-115 (71)	51-239 (151)	46-162 (83)

The figures in parentheses indicate the mean.

Flow Rate.—The flow rate was calculated according to the estimated basal oxygen requirements of the animals. Assuming a fixed arteriovenous oxygen difference, the flow rate is higher in animals with lower hemoglobins. Therefore flow rate is not only expressed in terms of cubic centimeters per kilogram per minute but also as grams hemoglobin per kilogram per minute. This concept of flow rate emerged when it was realized that a postoperative hypoxic syndrome developed during low flow perfusion and when it was found that the brain suffered hypoxia during low flow rates.[9] The details of this concept will be described elsewhere. The flow rates during these groups of experiments are shown in Table VI. The 2 animals in the ventricular fibrillation series that died were both perfused at 35 to 40 c.c. per kilogram per minute and at less than 6.0 grams hemoglobin per kilogram per minute. We believe that a postoperative hypoxic syndrome can be detected in animals when they are perfused at rates at or below their basal requirements. This is characterized by excessive oozing after perfusion, fall in arterial blood pressure which does not respond to blood transfusions, slow central nervous system response, and death within 12 to 48 hours after surgery.

TABLE VI. FLOW RATES DURING TOTAL PERFUSION

	CUBIC CENTIMETERS PER KILOGRAM PER MINUTE	GRAMS HEMOGLOBIN PER KILOGRAM PER MINUTE
Sinus rhythm	53-69	6.8-9.4
	(60)	(8.4)
Ventricular fibrillation	35-66	5.5-8.4
	(53)	(6.6)
Potassium citrate arrest	52-78	6.2-9.4
	(60)	(7.7)

The figures in parentheses indicate the mean.

DISCUSSION

Comparison of the data in the above groups of experiments indicates that in the majority of instances the variables before, during, and after perfusion did not differ significantly. The calculated flow rates based upon basal oxygen requirements and mixed donor and recipient hemoglobin are adequate for total body perfusions for periods of 45 to 60 minutes. We have not detected any deleterious effects resulting from perfusion with arterial blood having a tension of about 650 mm. Hg. The arterial pO_2 and pH can be precisely controlled by oxygenating blood with a combination of small and large bubble systems. In these experiments the pH of the arterial blood could be controlled within two hundredths of a pH unit. Although all these perfusions were done with arterial blood having a pO_2 of greater than 600 mm. Hg, it was possible to control this reading within 20 mm. Hg. In the majority of experiments, higher flow rates with high tension arterial blood resulted in higher venous oxygen saturations.

The left atrium was cannulated and kept at normal pressure during cardiac by-pass for the following reasons. (1) It has been found that the left atrial pressure may rise to dangerously high levels when the heart is released from potassium citrate arrest. (2) During cardiac arrest the blood in the pulmonary circulation has a high content of potassium. If this is not removed during

cardiac arrest, the blood with a high potassium content would be the first to perfuse the coronary circulation after release of the cardioplegia. (3) It appears that the incidence of postoperative pulmonary complications, including pulmonary collapse and hemorrhage, is decreased if the left atrial pressure is not elevated during total perfusion.

Although the various parameters related to the perfusion were comparable in the above groups, the striking difference was the high mortality rate in the experiments in which the heart was arrested with potassium citrate. As noted above, the common cause of death was failure of the heart to resume its normal rhythmicity after cardioplegia. In the animals that survived potassium citrate cardiac arrest, the immediate postoperative systemic blood pressures were lower than the other group of animals even though it was well maintained before and during total perfusion. The mechanisms for the high mortality rate in the potassium citrate group of dogs are not clear. Although extreme care was taken during the injection of the potassium citrate blood mixture into the ascending aorta after it had been cross-clamped, it is possible that an uneven distribution of the potassium citrate in the coronary circulation may explain some of the deaths. Another factor to be considered is that oxygen is still consumed by the arrested heart even though this may be at a much lower level than the beating heart. Preliminary studies by one of us (L. C. C.) indicate that isolated myocardium incubated with plasma containing similar amounts of potassium citrate as the Melrose blood solution[11] continues to consume oxygen at the same rate as myocardium incubated without added potassium.

It is appreciated that brilliant results have been obtained by arresting the human heart with potassium citrate during cardiopulmonary by-pass for treatment of intracardiac defects.[6] However, unexplained deaths with cardiac damage in humans have been recently reported after potassium citrate cardiac arrest. The discrepancy between the results in human and canine hearts may be due to a species difference. It is possible that the conductive system of the dog heart is more sensitive to mild oxygen deprivation as compard to the human heart. It is suggested that the ideal drug for cardioplegia should have a known and predictable reversible effect.

SUMMARY

1. The results of extracorporeal total body perfusion using potassium citrate cardiac arrest, induced ventricular fibrillation, and sinus rhythm in 40 dogs are compared.

2. Although the various parameters of the perfusion remained more or less constant in the above groups, the survival rate in the potassium citrate series was 50 per cent compared to 90 per cent in the animals where the heart was not arrested. The possible mechanisms of this difference are discussed.

3. The mechanism of death in the 2 animals in which cardioplegia was not used was due to an inadvertent low flow rate.

4. No deleterious effects were recognized in association with perfusion with arterial blood having a high oxygen tension.

5. Arterial blood pO_2 and pH can be precisely controlled using a combination of small and large bubble oxygenating system.

6. Decompression of the left atrium during cardiopulmonary by-pass is a reasonable precaution against postoperative pulmonary complications.

REFERENCES

1. Clark, L. C.: Monitor and Control of Blood and Tissue Oxygen Tensions, Tr. Am. Soc. Artificial Internal Organs 2: 41, 1956.
2. Clark, L. C., Gollan, F., and Gupta, V. W.: The Oxygenation of Blood by Gas Dispersion, Science 111: 85, 1950.
3. Clark, L. C., Helmsworth, J. A., Kaplan, S., Sherman, R. T., and Taylor, Z.: Polarographic Measurement of Oxygen Tension in Whole Blood and Tissues During Total Bypass of the Heart, Surg. Forum, Am. Coll. Surgeons, W. B. Saunders Company 4: 93, 1953.
4. Clark, L. C., Hooven, F., and Gollan, F.: A Large Capacity, All-Glass Dispersion Oxygenator and Pump, Rev. Scient. Instruments 23: 748, 1952.
5. Clark, L. C., Wolf, R., Granger, D., and Taylor, Z.: Continuous Recording of Blood Oxygen Tensions by Polarography, J. Appl. Physiol. 6: 189, 1953.
6. Effler, D. B., Groves, L. K., Sones, F. M., and Kolff, W. J.: Elective Cardiac Arrest in Open Heart Surgery: Report of Three Cases, Cleveland Clin. Quart. 23: 105, 1956.
7. Helmsworth, J. A., Clark, L. C., Kaplan, S., and Ford, C.: A New Method for the Drainage of Blood From the Open Heart During Total By-Pass of the Heart and Lungs, Surg. Forum, Am. Coll. Surgeons, W. B. Saunders Company 5: 35, 1954.
8. Helmsworth, J. A., Clark, L. C., Kaplan, S., Sherman, R. T., and Largen, T.: Artificial Oxygenation and Circulation During Complete By-Pass of the Heart, J. Thoracic Surg. 24: 117, 1952.
9. Kaplan, S., Matthews, E. C., Schwab, L., and Clark, L. C.: Oxygen Availability to the Brain During Inflow Occlusion of the Heart in Normothermia and Hypothermia, J. Thoracic Surg. 32: 576, 1956.
10. Kolff, W. J., Effler, D. B., Groves, L. K., Peereboom, G., Aoyama, S., and Sones, F. M.: Elective Cardiac Arrest by the Melrose Technic: Potassium Asystole for Experimental Cardiac Surgery, Cleveland Clin. Quart. 23: 98, 1956.
11. Melrose, D. G., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective Cardiac Arrest, Lancet 2: 21, 1955.

Discussion

(Papers by Lam, Gahagan, Mota, and Green; Kaplan, Clark, Matthews, Edwards, Schwab, and Helmsworth)

DR. DONALD B. EFFLER (Cleveland, Ohio).—Our experience with elective cardiac arrest has been confined to the Melrose technique utilizing potassium citrate. We have employed it in about 90 clinical cases and have made certain observations which I believe are significant. I think we can summarize our feelings by stating that elective cardiac arrest is the most important single advance in intracardiac surgery since the development of the cross circulation technique.

We have used elective cardiac arrest for periods as short as 6 minutes; the average duration is between 18 and 20 minutes, and the longest has been 59 minutes. As yet, we have seen no harmful effects that can be attributed to prolonged periods of cardiac arrest. The youngest patient in our experience was 10 months of age. The oldest was 59 years of age. We have used elective cardiac arrest for all types of open heart surgery with direct approaches in both the right and left heart.

Heart block has not been a major problem in our experience. We believe that heart block is related to localized myocardial anoxia that is aggravated by trauma and traction. If our concept is correct, heart block should be minimized by elective cardiac arrest accompanied by good perfusion.

Like Dr. Lam, we too have had our problems in the direct approach to tetralogy of Fallot. At present we have operated upon almost 20 of these patients and have found the major problem to be related to right ventricular outflow. In our early experience we did not use a prosthesis to close the ventricular septal defect, and the majority of these

reopened to some degree by subsequent catheterization studies. However, the most serious problem is that of eliminating ventricular outflow obstruction on the right side. It has been our practice to remove all of the abnormal papillary muscle and moderator bands that are present and to carefully inspect the pulmonary valve for additional valvular obstruction. This usually requires an incision directly through the annulus of the valve itself. However, the fact remains that the right ventricle in a true tetralogy is an "ugly one" and the desired surgical result may be difficult, if not impossible, to achieve. Our enthusiasm for operating upon the blue tetralogy is diminishing.

I would like to close by stating that elective cardiac arrest regardless of the type of drug employed is a tremendous adjunct in the field of open heart surgery.

DR. ORMAND C. JULIAN (Chicago, Ill.).—In view of our comparatively small experience in open heart surgery using the heart-lung machine, I would not offer discussion except that we have applied an idea which seems worth brief presentation. It occurred to us some time ago that patients with tetralogy of Fallot and those having pulmonary hypertension secondary to septal defects were particularly bad candidates for transverse bilateral thoracotomy. Because of their low pulmonary reserve and the changes in the pulmonary arterial tree, respectively, these patients particularly should be spared the partial collapse of both lungs and the postoperative difficulties of this type of incision.

Experience with 25 operations for aortic stenosis and pulmonary stenosis performed through a median sternotomy incision afforded an opportunity to study the anatomy of the mediastinal structures from this approach. This seemed ideally suited to intracardiac procedures using cardiac by-pass.

We have used this approach in 2 cases of interventricular septal defect, one of which was a tetralogy, and these have confirmed the impression that it is advantageous. The usual catheterization of the cavae through transatrial catheters was used. For inflow, a homologous artery of suitable size was attached by end-to-side anastomosis to the ascending aorta to form a side arm. The interventricular and interatrial septa and the right ventricular outflow tract are at least as easily exposed through appropriate cardotomy as they are with transverse incisions.

A partial list of the benefits to be gained with median sternotomy include: increased speed of exposure, less trauma to the rib cage and essentially total avoidance of incision or split in muscle tissue, improvement in exposure of the right ventricle because it is more superficially placed in the shallow wound, enlargement of the caliber of the arterial inflow with reduction in velocity and jet from a catheter, and, finally, complete avoidance of lung trauma and collapse.

We believe this incision to be worthy of attention.

DR. WILLIAM W. L. GLENN (New Haven, Conn.).—For some years we have been interested in the complication of air embolus in open heart surgery and several years ago described our experience in the deliberate use of ventricular fibrillation as a method of preventing air embolus and of obtaining a quiet heart. We were very much impressed in the experimental animal with the ease of resuscitation of the fibrillating heart which was supplied with oxygenated blood. Previous experimental work many years ago by Wiggers demonstrated that fibrillating hearts that were oxygenated could be made to revert to normal rhythm some 327 times in 328 attempts. The difficulty has arisen in using ventricular fibrillation in human open heart surgery from 2 points: one, the coronary flow is not controlled and, two, the human heart if well oxygenated is more difficult to keep in ventricular fibrillation than is the canine heart. There may be some advantage, however, to the perfusion of the coronary circulation with oxygenated blood during open heart surgery and it would seem at least for the present time that these studies on induced ventricular fibrillation should be continued. Perhaps time will prove that the cardiac perfusion agents will be entirely adequate for open heart surgery and that ventricular fibrillation with an oxygenated coronary flow will not be necessary.

DR. SAMUEL KAPLAN.—I would like to mention one point that was raised by Dr. Glenn pertaining to the use of ventricular fibrillation in the human heart. We too had experience in using this 4 years ago and also were struck by the fact the human heart is very difficult to keep in ventricular fibrillation. In addition we have found that coronary flow which still occurs when the heart is fibrillating may be no different in volume than that which occurs with normal sinus rhythm.

DR. CONRAD R. LAM (closing).—Dr. Effler has correctly emphasized the difficulties in open heart operations as applied to the tetralogy of Fallot. I am relieved to know that we are not the only ones having trouble. Dr. Julian's suggestion to make a midline sternal incision is certainly interesting, and except for cosmetic considerations it seems very attractive. Drs. Glenn and Deterling mentioned other methods of producing cardiac standstill, that is induced fibrillation and anoxia. Two years ago, we reported studies comparing these methods with potassium-induced arrest and found that at least in the hypothermic heart the induced arrest was superior (J. Thoracic Surg. 30: 620, 1955).

I would like to summarize by showing a final slide. We see the electrocardiographic tracings of 2 hearts, the one arrested with acetylcholine and the other with potassium citrate (Fig. 5). It is noted that during the arrest, there is some electrical activity of the acetylcholine-arrested heart, while there is no activity in the other heart. The recovery phase is longer in the potassium citrate heart. Evidently, the tendency to resume activity is not as strong.

LIGATION OF THE INFERIOR VENA CAVA FOR THROMBOEMBOLISM

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INTRODUCTION

DESPITE widespread interest in the prevention and treatment of venous thrombosis, it remains a common occurrence following operation, childbirth, trauma, and severe illness, as well as occasionally occurring in association with less usual lesions. Venous thrombosis itself causes considerable morbidity in both the early and late periods, but deaths are usually due to pulmonary embolism which occurs in certain unpredictable cases. Venous thrombosis at the same time produces nonlethal extremity symptoms and signs and threatens embolization to the lungs with the risk of death caused by the lung lesion added to the illness.

Anticoagulant drug therapy is generally accepted at present by many as the basis of treatment of venous thrombosis to prevent further clotting and limit venous damage as well as to prevent embolism. Previous hope that superficial femoral vein ligation would prove a simpler way to prevent embolism has not been justified. Such peripheral venous ligation is not always certain to prevent passage of a clot to the lungs and entails other disadvantages which often outweigh its merits. These disadvantages include blockade of the peripheral vascular drainage system with resultant venous hypertension of the extremities, although this is of little importance after ligation of the superficial femoral vein. Vein thrombosis often occurs distal to the ligation point. Whether the hypertension or the pre- or postligation venous thrombosis leads to leg pain, edema, varicosities, and ulcer is not completely clear, but these complications are common enough after certain vein ligations to constitute a real disadvantage. Further, a distal (femoral) venous ligation still may not prevent pulmonary embolism if the clot lies in the venous bed proximal to the ligation site (pelvic or prostatic veins) or if emboli pass around the ligation site via collaterals.

Many studies indicate the inability of superficial femoral ligation to prevent all embolism. Edwards and Robuck[17] concluded that superficial femoral vein ligation would fail to block emboli pathways in 10 per cent of the 61 extremities they dissected. Crutcher and Daniel[11] found that over 50 per cent of fatal emboli came from venous thrombosis above the inguinal ligament. Dehlinger and Riemenschneider[14] studied 74 autopsies of pulmonary embolism and concluded that ligation at the common femoral vein did not answer the

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problem because it had been helpful in only 15 of their cases, definitely of no value in 15, and questionable in 44. McLachlin and Paterson[26] in 100 autopsy dissections found that 73 per cent of the 34 venous thrombi found were in the thigh or pelvic veins and that superficial femoral vein ligation would have been too low in 21 per cent of the 34. Erb and Schumann[18] reported 100 fractures of the femoral neck. Nine of 50 treated by immediate superficial femoral vein ligation had pulmonary embolism while only 6 of the 50 nonligated cases had embolization in the lungs. Fowler and Bollinger[20] reported that venous thrombosis was the source of emboli in only 49 per cent of 97 cases (while the remainder were from the heart) and that only one-third of these originated in the legs.

Allen[1] in 1953 summarized 7 series of venous thrombosis and compared the series' 0 to 2.2 per cent mortality with the 0.52 per cent mortality at the Massachusetts General Hospital when femoral vein ligations were done. He further showed that while 0.55 per cent of 1,085 patients undergoing prophylactic femoral ligation died of embolism, none of 1,940 patients having prophylactic Dicumarol died (although 2 or 0.1 per cent of these died of hemorrhage).

The actual occurrence of pulmonary embolism after superficial vein ligation has confirmed these predictions. Anlyan and associates[2] reported several of these from Duke Hospital in 1952, and Ochsner[33] stated that this had occurred 11 times in his experience. Ravdin and Kirby[41] had 4 patients with emboli after superficial femoral vein ligation. It occurred to one of the patients presented in this paper.

These predicted and actual failures of femoral vein ligation when balanced against the results of anticoagulation therapy have indicated that its over-all results are no better than the reported results of anticoagulant therapy.*

The beliefs of Homans[22] expressed in 1949 still appear to summarize well the choice between anticoagulants and superficial femoral vein ligation. He concluded that while this ligation was harmless to the leg, it was insecure to absolutely prevent further embolism and so if used should be supported by anticoagulant drugs. Consideration of his cases of phlebothrombosis led him in general to plead for "treatment of venous thrombosis by anticoagulation with preservation of the common femoral pathway plus a carefully controlled scheme of physiotherapy."

In general I have followed this nonoperative management of venous thrombosis and pulmonary embolism, reserving vein ligations for cases where anticoagulants were contraindicated or had failed.

The place of inferior vena caval ligation in the management of thromboembolism has never been completely clear. The procedure has received a bad reputation because of reported leg complications, although it is generally recognized that it does prevent further pulmonary embolism. Ochsner,[33] for example, reported no further embolism after caval ligation in 60 cases. The smaller experience herein reported bears this out. Boyd,[5] however, did report

*The comments of Gage[21] and DeBakey[13] on the apparent variability of incidence of thromboembolism and the dangerous assumption that a given method has caused a changing incidence are recognized.

a patient with embolism after caval ligation, and it is thought that such will occur occasionally from the heart, from a site in the upper extremities, or via an anomalous inferior caval system.

Despite reports of the later sequelae of caval ligation in terms of leg pain, edema, varicosities, and ulcers, there are certain reports indicating that this need not occur if careful management is given to a cooperative patient. If this be true, the advantages of caval ligation in terms of certain immediate stoppage of embolization would suggest that the indications be broadened so that the cava would be ligated more frequently to control thromboembolism.

This report summarizes the information available in reported series of caval ligations and considers the results of the cases that I have followed with indications suggested in the light of this knowledge.

REPORTED RESULTS OF CAVAL LIGATION

While Kocher in 1883 and Billroth in 1885 had ligated the inferior vena cava because of operative trauma, their patients died. It remained for Bottini to perform the operation successfully first in 1893. Krotski found 48 reported cases in 1937.[32]

TABLE I. SUMMARY OF RECENTLY REPORTED LATE RESULTS OF INFERIOR VENA CAVAL LIGATIONS (SERIES SMALLER THAN 5 CASES OMITTED)

AUTHOR	REFERENCE	YEAR	CASES	LATER LEG RESULTS	FOLLOW-UP TIME
O'Neill	34	1945	8	Minimal discomfort	?
Northway and Buxton	32	1945	10	All edema requiring elastic support	1-12 mo.
Moses	30	1946	20	3 of 11 hospitalization survivors had edema	?
Thebaut and Ward	47	1947	34	9 of 32 hospital survivors had edema or varicosities	2-33 mo.
Connerley and Heintzelman	8	1949	10	Early swelling in all, no late swelling	?
Veal et al.	48 50	1947 1952	30	In general, all had edema	2-8 yr.
Shea and Robertson	45	1951	37	Only 1 of 25 followed had no leg sequelae	2-7 yr.
Poer	38	1951	11	1 persistent edema	?
Collins et al.	7	1951 1952	70	14 mild to two-plus edema	42 for 2 yr.
Zollinger and Teachnor	51	1952	20	Edema in 80 per cent followed, all working	to 5 yr.
Owens	35	1952	12	10 had some edema, all working	1-49 mo.
Payne	37	1953	5	No more than expected after phlebitis	?
Madden	27	1954	18	33 per cent edema, only 1 persistent	6 mo. to 7 yr.
Pratt	39	1954	40	No massive edema	?
Kirtley et al.	23	1955	34	Edema in 8 of 14 followed over 2 years, only 2 of 24 long-term survivors had limited activity	2 to 7 yr.
Bowers and Leb	4	1955	33	Persistent edema in 18 of 25 followed, 15 "good leg" ulcers developed	most, 5 yr.
Ochsner	33	1955	60	No details, infers no difficulty	?
Dale	Present	1957	16	Minor symptoms in all, major symptoms in 2	to 6⅔ year

Many different series of cases reported since then have been reviewed to determine not only the indications for caval ligation but also to learn what later leg sequelae have followed. Table I summarizes these cases with a brief account of conclusions regarding leg sequelae.

O'Neill[34] in 1945 reported 8 cases and indicated that edema usually ceased with the passage of time.

Northway and Buxton[32] in 1945 reported 10 caval ligations followed 1 to 12 months, all of whom had a variable degree of swelling after mobilization began. External elastic support controlled this in all patients.

Moses'[30] 1946 account of 20 cases of caval ligation with 11 surviving their total illness indicated that 8 of these 11 had no postoperative edema, although the follow-up time was not given.

Thebaut and Ward[47] presented their 34 instances of caval ligation in 1947. During the 2- to 33-month follow-up, 9 of the 32 survivors of the total illness had either edema or varicosities.

Cliffton and Neel[6] in 1949 gathered 136 reported cases and added 2. They showed the postoperative deaths in each series, which actually did not usually represent an operative mortality but indicated instead that the patient died during hospitalization.

Connerley and Heintzelman[8] in 1949 reported a series of venous ligations, including 10 of the vena cava for pulmonary embolism. They found early edema in all but no persistent edema.

Shea and Robertson[45] in 1951 reported 37 patients having caval ligation in Atlanta. Twenty-five were followed 2 to 7 years and only one was free of changes in his physical well-being and the status of the lower extremity in particular. Besides the edema which many developed, there were 10 patients with leg ulcers (4 bilateral). Poer[38] in commenting upon this series stated that results in the same city were better in 11 private patients in that only one of these had more then transient edema and inferred that patient cooperation was of great importance. The Shea and Robertson series is a later follow-up of the Thebaut and Ward series reported 4 years earlier in 1947. Deterioration occurred in the results during that period.

Collins and associates[7] in 1951 and 1952 in a series of several papers reported 70 female patients having caval and ovarian vein ligation for suppurative pelvic thrombophlebitis. Sixty-two survived the illness and 42 of these were followed over 2 years. Of the 62 survivors, 48 had no edema. The exact follow-up times are not given, but it is stated that 42 patients were followed for over 2 years. Ray and Burch[42] in 1947 reported studies on 12 of these patients and concluded that the circulatory adjustments were adequate and that there were no detrimental effects from ligation of the vena cava. Ochsner[33] brought this series to date in 1955 by reporting that Collins' series totaled 102 caval ligations without subsequent embolization. Details of the leg condition of the later cases are not given.

Zollinger and Teachnor[51] in 1952 reported 20 caval ligations of which 11 were performed prophylactically at the time of laparotomy and 9 were performed for venous pathology. Six died of carcinoma and one of myocardial

infarction later. Only 20 per cent of those followed up to 5 years had no edema and did not wear elastic stockings. However, all patients in whom recovery was expected returned to their normal duties.

Owens[35] in 1952 reported 12 cases followed one to 49 months, all of whom returned to work although some edema persisted in 10 patients and stasis ulcers occurred in 2. He believed these sequelae were due to the phlebitis and not to the ligation.

Veal[48, 50] in 1952 indicated in discussion that in general all of 30 patients who had had ligations 2 to 8 years before (and reported first in 1947) had bilateral edema for which they wore elastic stockings.

Payne[37] in 1953 reviewed the development of therapy for thrombophlebitis by both venous ligation and anticoagulation and concluded that the latter was in general the preferred treatment. He proposed 6 indications for caval ligation: (1) pulmonary embolism with unilateral iliofemoral or bilateral common femoral phlebitis, (2) pulmonary embolism without obvious source, (3) ascending venous thrombosis with anticoagulation contraindicated, (4) pelvic phlebitis with septic emboli, (5) ascending venous thrombosis uncontrollable by anticoagulants, and (6) blue phlebitis (phlegmasia cerulea dolens). Five cases were outlined. He felt that any edema was no more than expected from the phlebitis.

Pratt[39] reported no massive edema in over 40 caval ligations, although "some edema must be expected and accepted."

Madden[27] in 1954 presented the technical operative details clearly and briefly summarized results in 18 patients who had had ligations without death and followed 6 months to 7 years. There were 33 per cent with edema, although this was persistent in only one. Actual thrombectomy and division of the vena cava was shown in his drawings, although this is not usually necessary.

Kirtley, Riddell, and Hamilton[23] in 1955 carefully summarized the results of 34 caval ligations followed 2 to 7 years. Of 24 long-term survivors, 22 had no activity limitation due to leg symptoms, although 8 of 14 patients followed over 2 years did have edema. They suggested that patients without preligation leg signs had less difficulty after ligation because 7 of 10 preligation normal legs were normal after 2 years whereas only 3 of 7 phlebitic legs were normal.

Bowers and Leb,[4] however, concluded in 1955 that while sequelae of caval ligation were not dangerous, they were undesirable and would occur in about two-thirds of patients. All their 28 surviving patients showed edema after operation, and in 18 it was persistent: 3 times in the previously involved leg, once in the "good" leg, and 14 times in both legs. Fifteen ulcers developed in the "good" leg after operation.

Table I summarizes these recent series of 5 or more reported by American surgeons. Specifically omitted are many reports of caval ligation for congestive heart failure from Europe and South America because the basic disease is quite different in those reports. Despite the fact that these series date back to 1945, there are few cases followed carefully for long periods and 8 years appears to the

maximum follow-up period. Furthermore, many of the results are covered by general statements without details of individual follow-ups. Despite wide variation in reports, certain impressions are gained.

It appears that edema has occurred more often than not. Whether this is persistent for years or whether it improves (or worsens) is not always clear, but there are multiple statements indicating the use of elastic external supports and inferring that patient cooperation is important. Reports of return to former occupation or to useful employment imply that some degree of handicap has been overcome. On the other hand, the reports of skin ulcers in the legs were fewer than anticipated, and it appears that this ordinarily was not a problem.

SUMMARY OF CASES

Summarized in Table II are the 16 patients who have eventually required caval ligation in this hospital to date. Appreciation is expressed to several attending surgeons including Drs. W. J. M. Scott, E. B. Mahoney, and C. D. Sherman, who with the author and members of the resident staff performed the actual operations and follow-up studies.

Histories of these 16 patients illustrate the variability of the onset of thromboembolism. The most unusual was the 23-year-old medical student whose initial leg signs followed driving an auto a long distance on the New York State Thruway for many hours. This, along with 2 other similar cases of phlebitis seen personally and several occurring in the practice of other physicians here, has led to the term "Thruway Thrombosis." Venous thrombosis closely following such an auto trip where the patient sits with legs flexed and unmoving for many hours clearly implicates immobility and the flexed position as a cause in an otherwise healthy person. There were 5 other cases where no known illness or trauma preceded the thrombophlebitis, and actually only 5 of the cases followed trauma or operation.

Leg signs were found at some time in every patient, although at times this occurred after pulmonary embolism. Although several were diagnostic problems originally, all eventually developed typical leg and chest signs.

All patients except 3 received anticoagulant therapy prior to caval ligation, and 6 patients had more than one course. Operative indications may be summarized as 12 cases of recurrent embolism after anticoagulant drugs, one case of high proximal venous thrombosis, one case of drug contraindication, and 2 cases of embolization without trial of drugs. One patient had repeated embolism after both anticoagulants and bilateral superficial femoral vein ligations had been performed.

There were no further embolisms or deaths following caval ligation although one patient (H. G.) died 85 days later with rectal carcinoma and empyema secondary to degeneration of a pulmonary infarct (due to preligation embolism). No mortality, therefore, is attributed to the operation.

All except 2 patients exhibited some degree of leg edema in the early postoperative period. This was not a great problem after a few days. Ten patients have had no late edema while 6 patients have had edema. The over-all

TABLE II. SUMMARY OF 16

NUMBER	PATIENT	AGE SEX	DATE	HISTORY	LEG SIGNS		CHEST SIGNS			
					PAIN	EDEMA	HEMOPTYSIS	PAIN	X-RAY	RUB
1.	E. K. 313406	28 M	8-21-50	18 days after umbilical herniorraphy	+	0	0	+	+	0
2.	L. T. 306299	49 F	10- 4-50	Phlebitis and recurrent embolism	+	+	+	+	0	0
3.	F. C. 202830	77 M	5- 2-52	Phlebitis and recurrent embolism, 3 months	+	+	0	+	+	+
4.	F. D. 341048	41 M	5-17-52	Recurrent embolism after open reduction tibia	+	+	+	+	0	+
5.	H. L. 297216	41 M	1- 2-53	Phlebitis after varicella with embolism	+	+	+	+	+	+
6.	A. Y. 352832	33 M	12-24-42	Lacerated knee, phlebitis, recurrent embolism	+	+	+	+	+	0
7.	H. G. 390336	70 M	2- 2-55	Pancreatitis and cancer of the rectum	+	+	+	+	+	0
8.	G. B. 83914	63 M	2- 3-55	Phlebitis with embolism after U.R.I.	+	+	0	+	+	+
9.	F. C. 359548	72 M	3-10-55	2 weeks after umbilical hernia and 1 week after g. b.	+	+	+	+	0	0
10.	O. B. 391681	42 F	8-20-55	10 months migratory phlebitis and emboli	+	+	+	+	+	0
11.	R. C. 201063	23 M	9-26-55	"Thruway thrombosis" and emboli, 1 year	+	+	+	+	+	+
12.	A. S. 296520	33 F	7-20-56	5 years phlebitis and embolism	+	+	+	+	+	+
13.	H. F. 420463	70 M	12-31-56	4 days after prostatectomy	+	+	0	0	0	0
14.	M. M. 429331	31 F	1-27-57	Recurrent embolism, 5 years since pregnancy	+	+	0	+	0	0
15.	J. R. 429595	71 M	2- 2-57	Sudden painless edema, 48 hours	0	+	0	0	0	0
16.	A. D. GH46040	30 M	4-18-57	2 embolisms after fractured femur	+	+	+	+	+	?

leg results are good in that 14 cooperative patients have returned to their occupations and are in no sense invalids. On the other hand, their legs are not completely normal. Several who have no demonstrable edema do develop a tight feeling if they stress the legs by hard or prolonged exercise. Of the 11 patients who have been followed beyond 10 months, there are 4 with some form of edema or ulcer and at least 2 others have pain on exertion or during damp, cold weather. The leg results are therefore far from normal. However, it is felt that the operative indications in this series were strong and that the advantages in terms of life salvage and cessation of illness completely outweigh the slight leg disadvantages for these cooperative patients. The single noncooperative patient makes it clear why such individuals show poorer leg results.

INDICATIONS FOR CAVAL LIGATION

In general, the management of venous thrombosis* has been nonoperative and based upon anticoagulant drugs. Venous ligation has been reserved for the

*While separation of cases into those representing thrombophlebitis and phlebothrombosis is helpful regarding symptoms and signs and prognosis, it is thought that they represent different stages of venous thrombosis and hence this latter term is preferred.

CASES (TO MAY 1, 1957)

GENERAL			RESULTS						
SHOCK	DYSPNEA	ANTICOAGULANTS	EARLY EDEMA	LATE EDEMA	VARICOSITIES	ULCERS	EARLY HEMATURIA	COOPERATION	FOLLOW-UP
+	+	6 days	+	0	0	0	+	Good	6⅔ yr.
0	0	0	+	?	0	0	0	Poor	1 yr.
0	0	2 courses	+	0	0	0	+	Good	11 mo.
0	0	2 courses	+	+	0	0	0	Poor	2⅓ yr.
+	+	2 courses	0	0	0	0	0	Good	4⅓ yr.
0	0	9 days	+	0	0	0	0	Good	4⅓ yr.
0	+	2 days	0	0	0	0	0	Good	Died, 85 days
0	0	20 days	+	sl.	+	+	0	Good	2⅙ yr.
0	+	1 day	+	+	0	0	0	Good	2 yr.
0	+	0	+	0	0	0	0	Good	20 mo.
0	+	2 courses	+	0	0	0	0	Good	20 mo.
0	+	Several courses	+	sl.	0	0	0	Good	10 mo.
0	0	Contraindicated	sl.	0	0	0	0	Good	4 mo.
0	+	4 courses	+	+	0	0	0	Good	3 mo.
0	0	12 hours	+	sl.	0	0	0	Good	3 mo.
0	+	Yes	+	–	–	–	–	Good	12 days

occasional case in which anticoagulants have failed or are contraindicated. Our most recent study of autopsy experience here indicated no changes in this general policy.

All 527 autopsies for 1952 were surveyed and 67 (13 per cent) of those patients were found to have pulmonary embolism in some form. The clinical records of those 67 patients were then studied. In only 2 instances had there been a diagnosis of pulmonary embolism with anticoagulant therapy of this prior to death. Other patients either died without diagnosis or too quickly for treatment. These 2 patients, therefore, represent failure of anticoagulation therapy whereas the 65 other deaths represent failure of diagnosis, minor embolism, or death before any treatment could be given. The treatment plan may be summarized as follows:

I. Superficial or Saphenous Vein Thrombosis

A. Rest, elevation, heat, Aces

B. If progressive toward femoral junction, ligate saphenous

II. Deep Venous Thrombosis With or Without Embolism

A. Rest, elevation, anticoagulants, Aces when up (heat and paravertebral block for some)

B. Thrombosis above superficial femoral level, ligate cava

C. Embolism during or after anticoagulants, ligate cava

D. Anticoagulants contraindicated, caval ligation

Some patients with minor superficial vein thrombosis require little or no treatment, and partial restriction of activity, elevation, and heat will suffice to treat minor varieties without hospitalization. However, if the phlebitis spreads up the saphenous vein toward the femoral, it is advisable to ligate the saphenous vein.

Patients with severe superficial or any type of deep venous thrombosis have been given anticoagulant therapy immediately by means of a 50 mg. intravenous dose of heparin, and further depo-heparin doses on the basis of a scheme modified from McCleery and Yarborough.[25] The clotting time has been thus elevated toward a planned 20- to 60-minute level. At the same time a long-acting anticoagulant in the form of Tromexan has been administered to attempt maintenance of prothrombin time between 20 and 40 per cent. Heparin is stopped once this level is reached, ordinarily in one to 3 days. It is then planned to continue Tromexan anticoagulation therapy for 28 days since pulmonary embolization after that time is unusual, although it may and did occur in this series. Bed rest to prevent unnecessary activity until the existent clot begins to organize and attach to the vein wall is continued for 5 days and elastic wrappings are used from toes to knees on both legs when ambulation occurs. These are continued for 6 weeks to prevent edema at any time.

Paravertebral block is at present reserved chiefly for acute thrombophlebitis with considerable pain, edema, and fever. It is not used in conjunction with pre-existing anticoagulation for fear of hemorrhage, although Pratt[39] reported 2,152 blocks in 566 patients on anticoagulants without overt hemorrhage. If it appears desirable to block sympathetics and also use anticoagulant drugs, it is advisable to place an indwelling epidural catheter to be used for repeated procaine injections and only after it is placed to start anticoagulant drugs.

Patients who initially present *after* lung embolism are at once placed on this program and receive the same treatment as if they had had only venous thrombosis without embolism. Venous ligation has not ordinarily been used prior to anticoagulant therapy.

When anticoagulant therapy is contraindicated in a patient who has not had embolism, the treatment consists of bed rest, elevation, and in some cases, paravertebral block. If embolism has already occurred, a venous ligation is done at once.

A few patients in this series were ligated with absorbable gut in the hope that recanalization of the cava with lowering of venous hypertension in the legs would occur as it did in a series of dogs.[12] The brief follow-up period on these patients does not allow conclusions yet. If the deligation proves feasible,

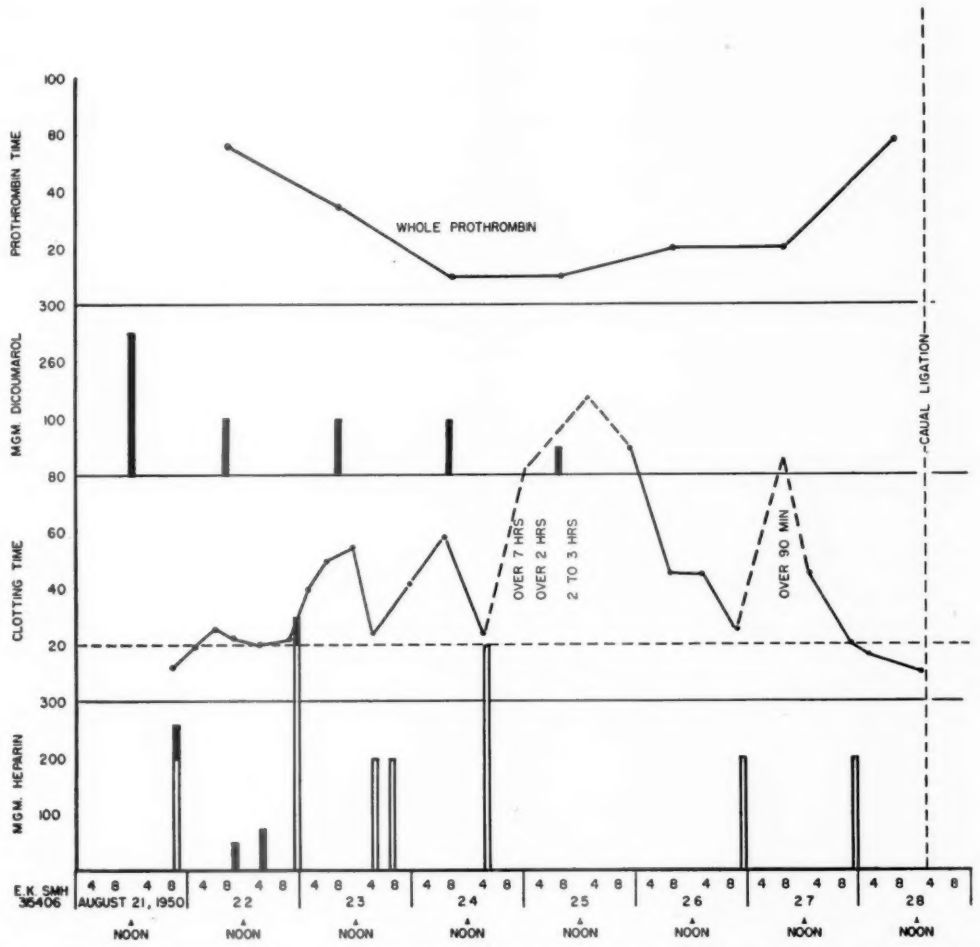

Fig. 1.—Clinical course of Patient E. K. Recurrent embolism occurred August 27 despite adequate anticoagulation therapy.

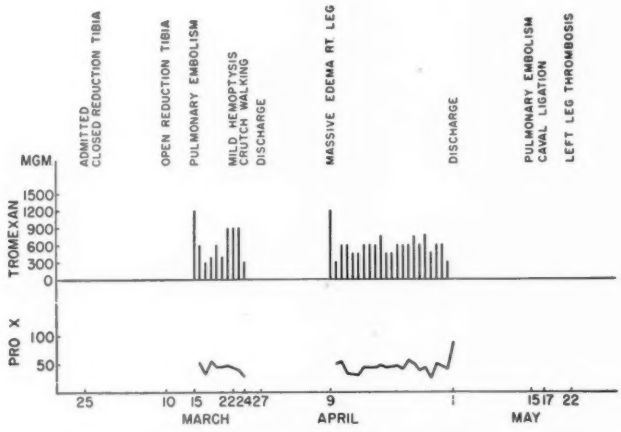

Fig. 2.—Clinical course of Patient F. D. Recurrent embolism occurred after 2 courses of anticoagulants.

the indications for caval ligation could be widened. Also, if further studies such as this show that the long-term leg results continue to be acceptable, the indications can be extended.

Summary of these indications shows that the inferior vena cava has not been ligated for embolism unless anticoagulants have failed or could not be

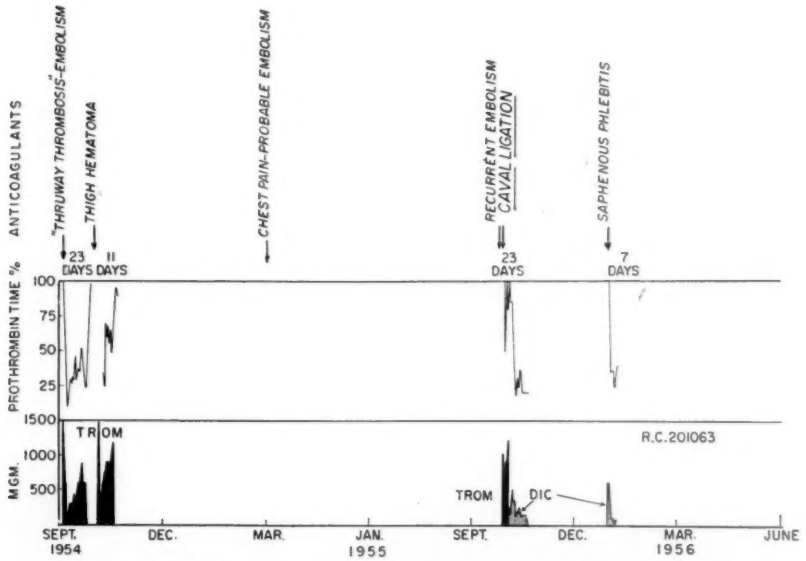

Fig. 3.—Clinical course of Patient R. C. Recurrent embolism necessitated caval ligation since anticoagulant therapy had failed. Anticoagulants were used after operation also.

Fig. 4.—Saphenous venogram of Patient J. R. showing defect due to clot in femoral vein at lower arrow.

used or unless the thrombosis was above the superficial femoral vein level. To these indications may be added pelvic phlebitis with septic embolism of the type reported by Collins and associates.[7] Whether blue phlebitis (phlegmasia cerulea dolens) is best treated by caval ligation[28] or by sympathetic nerve block, elevation, and exercise[49] is not yet known. Case 15 verged on this type of venous thrombosis. This patient, as well as another patient with a true case of blue phlebitis (treated elsewhere and not included here), had caval ligation and femoral vein thrombectomy with satisfactory results. Two other cases, managed by colleagues, were treated without operation with satisfaction. Figs. 1 to 4 show typical cases in this series. Fig. 1 shows the failure of adequate anticoagulation therapy to prevent recurrence of embolism, leading to caval ligation for patient A. Y.

Fig. 2 shows how 2 courses of anticoagulants were used for patient F. D. with later recurrence indicating caval ligation. Neither course was as long as would be currently used.

Fig. 3 illustrates patient R. C., a medical student, who had recurrence of embolism a year after anticoagulant therapy and who at present is doing well as a surgical resident.

Fig. 4 shows the phlebogram of patient J. R. who had venous thrombosis without embolism. The thrombosis extended into the iliac system as demonstrated by the phlebogram and at venous thrombectomy done just after caval ligation.

OPERATIVE TECHNIQUE

Thirteen of these cases were operated upon via the extraperitoneal approach from the right. Three were approached transperitoneally, once in order to remove the ovaries, once in order to explore the iliac veins, and once early in the series as a purely elective approach. However, the usual exposure is similar to that for lumbar sympathectomy on the right through a somewhat oblique transverse incision splitting the muscles and entering the extraperitoneal space by pushing the peritoneal sac medially. The genitofemoral nerve is particularly protected from the trauma of retractors and instruments to avoid the painful anterior thigh neuritis which may follow such. Sufficient split in the fascia overlying the vena cava should be made to allow safe dissection about its circumference. While the lumbar veins on the right side are seen and easily avoided, the left lumbar veins and anomalies discussed in the following section present a hemorrhage hazard. In the event that such a contralateral vein tear occurs, the area may be packed for 3 to 5 minutes or bleeding controlled by caudad ligation of the cava which causes the proximal venous pressure to decrease.

Permanent caval ligation is done with 2 heavy nonabsorbable ligatures of 2-0 silk. Cutting the cava between such ties is dangerous and unnecessary. Nonpermanent ligation of the inferior vena cava in the form of a single absorbable 2-0 gut tie has been used for a few patients suffering embolism directly after trauma, operation, or childbirth when it is to be expected that there will not be recurrence after the present venous thrombosis heals. Such

temporary ligation is based upon experimental results[12] and has not to date been finally evaluated clinically. It is aimed at prevention of long-term venous hypertension in the legs as a result of permanent vena caval ligation.

INFERIOR VENA CAVAL ANOMALIES

Many variations of the inferior vena cava have been found during autopsy or cadaver dissection. Anson[3] has been quoted to the effect that left-sided vena cava was found 4 times in 33 cadavers one year and once in 33 the next year. Edwards[16] investigated the variations and anomalies of the inferior vena cava and found 5 such in 33 human beings consecutively studied. Besides the reported double and left-sided cavae, he showed examples of a preureteric caval position and of a pelvic kidney with low entry of that renal vein into the hypogastric vein.

Absence of the inferior vena cava on the right or small size should at once suggest anomaly. Encountering an obstacle upon attempting to pass a ligature suggests not only a normal lumbar vein but also a caval variation indicating a safer ligation if done more caudad. Intravenous pyelography may be done to rule out pelvic kidney. Only rarely has such variation been recognized clinically, such as the left-sided cava found by Crutcher[10] at secondary left-sided operation. The frequency of variation in consecutive dissection room series makes it seem likely that some are not recognized during the course of the usual caval ligation when only about an inch of the vessel is visualized. Passage of emboli through the left side of a double cava or through some other variation may explain pulmonary embolism after caval ligation, as in a case reported by Boyd.[5]

While no such variation has been recognized in the series herein reported, the staff pathologists have rarely seen such. I have seen 2 double cavae in dogs with only one side ligated and the other side unrecognized until a venogram was made.[12] These experiences allow understanding of how such anomalies are overlooked in human beings.

COLLATERAL CIRCULATION

There are numerous venous collaterals which carry blood toward the heart following ligation of the inferior vena cava. Northway and Buxton[32] emphasized the vertebral communications of these collaterals while Robinson[43] reviewed previous reports of animal as well as human collateral circulation and made injection preparations of 8 stillborn infants. Surington and Jonas[46] made phlebograms by passing a polyethylene catheter up through the saphenous vein to allow injection of radiopaque material 2 to 3½ years after caval ligation in 3 patients and other studies of temporarily occluded cavae during lumber sympathectomy. The principal collateral pathways found were (1) the ascending lumbar veins, (2) vertebral veins, (3) ovarian veins, (4) ureteral veins, and of least importance, (5) the superficial trunk veins.

The importance of the vertebral system has been stressed by these authors. Animal experiments tend to bear this out since it was found that the vertebral

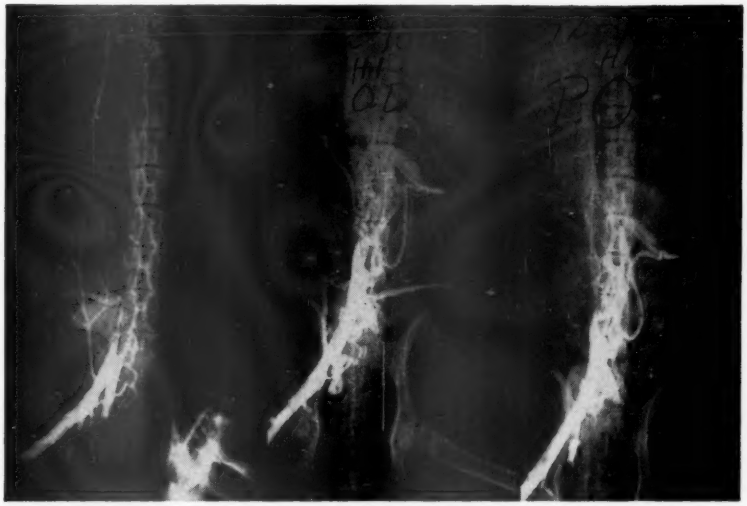

Fig. 5.—Dog venograms on third, forty-fifth, and one-hundred-forty-second day after ligation of cava to illustrate immediate presence of vertebral vein collaterals (left) and change of other collaterals from a network of fine veins (left) to a few large dilated ones (right).

Fig. 6.—Venogram of Patient H. L. 18 months after caval ligation (marked by 2 clips). Arrow shows superior reconstitution of cava via collaterals (visualized by dye on right side of patient).

veins fill at once after caval ligation while the other systems show slow dilatation.[40] Fig. 5 shows dog phlebograms made at 3, 45, and 142 days after the vena cava was tied. The vertebral loops are clearly seen as large collaterals at 3 days while the other collateral circulation slowly enlarged.

Human phlebograms to date have been difficult for us to make. Fig. 6 illustrates one such where the dye passes upward via dilated tortuous collaterals.

VENOUS PRESSURE STUDIES

Occasional deaths have followed caval ligation as collected by Moretz and associates.[29] The probable explanation is venous pooling with inadequate venous return to the heart. Such deaths are well recognized in the dog after caval ligation. In an effort to determine whether study of the venous pressure will allow prediction of such a death, a series of these has been done in patients similar to that already reported by us in dogs.[12]

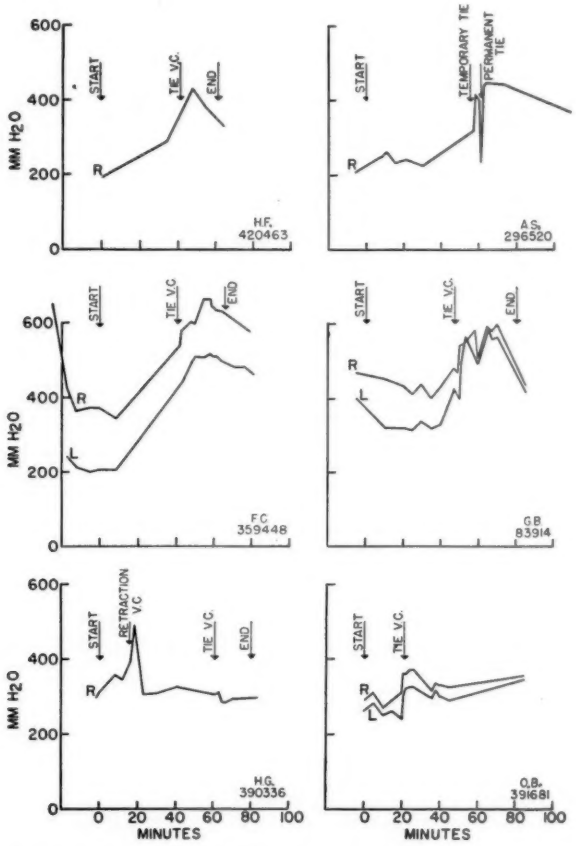

Fig. 7.—Saphenous venous pressure studies of 6 patients. Pressure recorded from top of operating table mattress. See text for interpretation.

In brief, a No. 18 needle was placed into the saphenous vein at the ankle and connected to a saline manometer to allow venous pressure determinations to be made at intervals. Animal investigation showed that with the subject flat, the saphenous and iliac pressures are approximately equal, provided no obstruction intervenes, and it is assumed the same is true of human beings.

Fig. 7 shows 6 such studies and is essentially self-explanatory. It will be seen that in the 3 cases where both legs were studied simultaneously the changes paralleled each other; although if one leg was involved with phlebitis, that leg might show a different absolute pressure.

The plot of patient H. G. shows how pressure over the vena cava with a retractor elevated the pressure while the actual ligation did not. It is likely that collaterals opened rapidly in that case. Patient A. S. had temporary venous occlusion and release prior to final ligation.

In general, there is a rise in venous pressure following caval ligation, but none of these cases rose to alarming levels. A rather rapid pressure decrease followed. None of these pressures rose to the alarming levels seen in some dogs. However, the pressures in Case 15, which are not shown, started at 600 mm. of water in the involved leg and went over 1,000 mm. at caval ligation. This patient had the most severe and extensive thrombosis of the entire series.

No conclusions have been made yet regarding these studies. They are reported chiefly to show the method.

POSTOPERATIVE MANAGEMENT

The principles of postoperative management may be outlined as follows: (1) Prevention of edema: (a) elevation of foot of bed, (b) Ace bandages whenever out of bed, (c) graded walking when pain permits, (d) restriction of ambulation if edema occurs, (e) restriction of sitting or standing, (f) Aeropulse boots, and (g) contour chair. (2) Prevention of further thrombosis: (a) anticoagulants and (b) thrombectomy if it occurs. (3) Pain control: (a) medication and (b) elevation of legs. (4) Maintenance of muscle power: program of weighted exercises for calves and thighs.

The importance of *preventing edema* should be impressed upon the patient immediately and at each successive visit. Edema with consequent stretching of the skin and eventual disrupting of elastic fibers leads to a vicious cycle eventuating in boggy tissues which are prone to infection and ulceration besides being uncomfortable and moderately disabling from the standpoint of weight alone. It is immediately proposed to the patient that no edema shall be permitted at any time and that with his cooperation such is possible after a few days. Ambulation should not begin until there is no leg edema, and if it occurs in the immediate postoperative period it should be combatted not only by the placement of Ace bandages while the patient is in bed but also by elevation of the extremities above the level of the heart. Ordinarily, this results in a rapid return of the legs to a nonedematous state, and severe edema should raise the question of widespread thrombosis which might be improved by a venous thrombectomy.

When the patient becomes ambulatory, Ace bandages should be firmly placed from toes to knees, and the patient should walk while he is out of bed rather than sit. A recommendation is made that he obtain a contour-type chair so that he can rock back and elevate the feet above the heart level when he is sitting at home.

While Ace bandages are perfectly adequate for control of swelling in the immediate postoperative period if they are relatively new and if they are

applied properly, it has been found that a special legging (Aero-pulse boot[44] in Fig. 8) is considerably easier for the patient to use and that it is more efficient in preventing edema. Certain patients who have been thought nonedematous while wearing Ace bandages have been observed to decrease the leg size immediately when they were placed in Aero-pulse boots. Fig. 9 shows new normal nail growth proximal to older abnormal growth in a patient (F. C.) placed in Aero-pulse boots several months after operation. The improved nail nutrition indicates the benefits from the leggings. These boots are, therefore, ordered for both legs of each patient in the early postoperative period, and the patient is told that they may be needed for a period of several months up to a year or longer. After the legs have been completely asymptomatic in regard to pain and swelling (which may be from 3 months to a year or longer), he is instructed to remove the boots each day when he returns from work. If no edema occurs by bedtime over a period of a month, he is asked to remove the boots at an earlier hour and this graded removal continues until he is able to do without them completely. Should edema occur at any time, however, the patient is placed back into the boots for another 3- to 6-month period until the collateral circulation is improved and until no edema follows their removal.

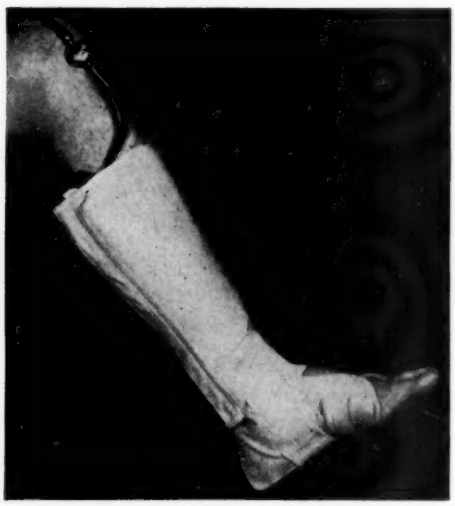

Fig. 8.

Fig. 9.

Fig. 8.—Aero-pulse boot.[44]
Fig. 9.—New nail growth (proximal portions pushing distal older veins off) associated with better nutrition of foot of Patient F. C. after wearing Aero-pulse boot.

Prevention of further thrombosis is attempted by continued anticoagulant therapy instituted in the immediate postoperative period. Animal experiments have shown that while postoperative thrombosis in a vein distal to the ligatures is a usual occurrence (at least in dogs) this can be prevented by the immediate use of an anticoagulant such as Tromexan.[12]

Venous thrombectomy has been used occasionally in the management of venous thrombosis and a small personal experience of only 2 cases indicates it to be worthy of further trial.

Pain control is ordinarily dependent upon elevation and drugs rather than paravertebral procaine blocks. Venous thrombectomy with removal of clot also relieves pain.

Maintenance of muscle power must not be overlooked following vena caval ligation. A detailed program of active exercise is outlined to each patient and a written record is kept by the patient in order to promote recovery of muscle power rapidly.

DISCUSSION

The therapy of thromboembolism is still obscured by large defects in knowledge of its etiology and natural history. The numerous prophylactic and therapeutic regimens proposed and tried attest to this, and there is considerable evidence that there has been no real decrease in the incidence of the disease for many years. Despite early enthusiasm for a succession of prophylactic measures such as early ambulation, Ace bandages, and leg exercises, there is no convincing evidence that any of these has truly changed the pattern. The effectiveness of intermittent anticoagulation as used by the Swedes has even been questioned.[13]

While prophylaxis is uncertain, therapy of established disease has resulted in lower morbidity and mortality. Careful and adequate anticoagulation therapy or venous ligation has resulted in fewer fatal pulmonary embolisms. Anticoagulants at present appear to have resulted in as good protection as femoral ligation, although neither offers 100 per cent assurance. Inferior vena caval ligation approaches such 100 per cent assurance of embolism control, yet results in a significant number of abnormal legs as late results. Whether this number is greater than would be expected from the phlebitis if not treated by caval ligation is unknown and comparative figures are needed. However, for the present it does not appear justified to subject large groups of patients to caval ligation in order to protect the occasional one who will not be controlled by drugs alone. Rather it appears proper to reserve caval ligation for failure of or resistance to anticoagulant drugs, plus certain other less frequent indications. These patients would then undergo an operation to prevent embolism after failure of nonoperative treatment. The leg price can thus be reduced to a reasonable one by an interested physician dealing with a cooperative patient. In the absence of patient cooperation or close supervision, the results are apt to be considerably worse.

The careful postoperative management of the legs is chiefly aimed at prevention of edema. Clinical experience has indicated that the methods described here are practical and effective in preventing serious leg complications but that minor abnormalities continue to occur.

CONCLUSIONS

1. The clinical management of 16 instances of inferior vena caval ligation for thromboembolism is discussed against the background of experience reported in the literature.

2. There was no operative mortality nor further embolism. While early postoperative leg edema was usual, the late leg complications proved to be minor

if the legs were carefully managed. Three of 9 followed beyond 10 months have some edema or ulcer of the legs, although no patient has been incapacitated.

3. Anticoagulant drug therapy is advocated for venous thrombosis and/or pulmonary embolism in general. Inferior vena caval ligation (rather than superficial femoral vein ligation) should be reserved for (a) failure of anticoagulant therapy, (b) contraindication to anticoagulants, and (c) thrombosis of pelvic veins (iliac, ovarian, prostatic, and so forth). Rare indications include septic pelvic phlebitis and phlegmasia cerulea dolens.

4. Operative technique and vena caval anomalies are discussed.

5. Details of postoperative leg management are emphasized and are chiefly directed toward prevention of edema at any time.

REFERENCES

1. Allen, A. W.: Management of Thromboembolic Disease in Surgical Patients, Surg., Gynec. & Obst. **96:** 107, 1953.
2. Anlyan, W. G., Campbell, F. H., Shingleton, W. H., and Gardner, C. E.: Pulmonary Embolism Following Venous Ligation, A. M. A. Arch. Surg. **64:** 200, 1952.
3. Anson, B.: Personal communication.
4. Bowers, R. F., and Leb, S. M.: Late Results of Inferior Vena Cava Ligation, SURGERY **37:** 622, 1955.
5. Boyd, D. P.: Ligation of the Inferior Vena Cava, Lahey Clin. Bull. **1:** 152, 1951.
6. Cliffton, E. E., and Neel, J. C.: Ligation of the Vena Cava in Extending Thrombophlebitis, Arch. Surg. **59:** 1122, 1949.
7. Collins, C. G., MacCallum, E. A., Nelson, E. W., Weinstein, B. B., and Collins, J. H.: Suppurative Pelvic Thrombophlebitis, SURGERY **30:** 298, 1951.
8. Connerley, M. L., and Heintzelman, J. H. C.: Treatment and Prophylaxis of Pulmonary Embolism by Vein Interruption, New England J. Med. **240:** 830, 1949.
9. Crane, C.: The Use of Heparin-Gelatin-Dextrose in Venous Thrombosis and Pulmonary Embolism, New England J. Med. **245:** 926, 1951.
10. Crutcher, R. R.: Discussion, Ann. Surg. **141:** 663, 1955.
11. Crutcher, R. R., and Daniel, R. A.: Pulmonary Embolism—a Correlation of Clinical and Autopsy Studies, SURGERY **23:** 47, 1948.
12. Dale, W. A., Pualwan, F., and Bauer, F. M.: Ligation of the Inferior Vena Cava With Absorbable Gut, Surg., Gynec. & Obst. **102:** 517, 1956.
13. DeBakey, M. E.: A Critical Evaluation of the Problem of Thromboembolism, Internat. Abst. Surg. **98:** 1, 1954.
14. Dehlinger, K., and Riemenschneider, P.: Pulmonary Embolism, New England J. Med. **240:** 497, 1949.
15. DeTakats, G.: Anticoagulant Treatment in Surgery, J. A. M. A. **142:** 527, 1950.
16. Edwards, E. A.: Clinical Anatomy of Lesser Variations of the Inferior Vena Cava; and a Proposal for Classifying the Anomalies of This Vessel, Angiology **2:** 85, 1951.
17. Edwards, E. A., and Robuck, J. D.: Applied Anatomy of the Femoral Vein and Its Tributaries, Surg., Gynec. & Obst. **85:** 547, 1947.
18. Erb, W. M., and Schumann, F.: An Appraisal of Bilateral Superficial Femoral Vein Ligation in Preventing Pulmonary Embolism, SURGERY **29:** 819, 1951.
19. Foley, F. E. B., Richardson, E. W., Mulvaney, W. P., and Victor, I.: Massive Electrocoagulation of Deeply Infiltrating Bladder Tumors Combined With Ligation of the Vena Cava for Prevention of Pulmonary Embolism, J. Urol. **70:** 456, 1953.
20. Fowler, E. R., and Bollinger, J. A.: Pulmonary Embolism—A Clinical Study of 97 Fatal Cases, SURGERY **36:** 650, 1954.
21. Gage, Mims: Thromboembolic Phenomenon—Local Process With Regional Spread and Systemic Complications, Ann. Surg. **137:** 577, 1953.
22. Homans, J.: Venous Thrombosis, SURGERY **26:** 8, 1949.
23. Kirtley, J. A., Riddell, D. H., and Hamilton, E. C.: Indications and Late Results of Ligation of Inferior Vena Cava, Ann. Surg. **141:** 653, 1955.
24. Kistner, R. W., and Smith, G.: A Ten-Year Analysis of Thromboembolism and Dicumarol Prophylaxis, Surg., Gynec. & Obst. **98:** 437, 1954.
25. McCleery, R. S., and Yarborough, J. A.: A New Tolerance Test as a Guide to Clinical Heparin Therapy, Circulation **4:** 394, 1951.
26. McLachlin, J., and Paterson, J. C.: Some Basic Observations on Venous Thrombosis and Pulmonary Embolism, Surg., Gynec. & Obst. **93:** 1, 1951.

27. Madden, J. L.: Ligation of the Inferior Vena Cava, Ann. Surg. **140**: 200, 1954.
28. Miles, R. M.: Phlegmasia Cerulea Dolens—Successful Treatment by Vena Cava Ligation, SURGERY **30**: 718, 1951.
29. Moretz, W. H., Naisbitt, P. F., and Stevenson, G. P.: Experimental Studies on Temporary Occlusion of the Inferior Vena Cava, SURGERY **36**: 384, 1954.
30. Moses, W. R.: Ligation of the Inferior Vena Cava or Iliac Veins—A Report of 36 Operations, New England J. Med. **235**: 1, 1946.
31. Murray, G.: Anticoagulants in Venous Thrombosis and the Prevention of Pulmonary Embolism, Surg., Gynec. & Obst. **84**: 665, 1947.
32. Northway, R. O., and Buxton, R. W.: Caval Ligation in Phlebothrombosis, SURGERY **18**: 85, 1945.
33. Ochsner, A.: Discussion of Kirtley, et. al.: Ann. Surg. **141**: 661, 1955.
34. O'Neill, E. E.: Vena Caval Ligation for Phlebothrombosis, New England J. Med. **232**: 641, 1945.
35. Owens, F. M.: Vena Caval Ligation in Thromboembolic Disease, A. M. A. Arch. Surg. **65**: 600, 1952.
36. Paterson, J. C., and McLachlin, J.: Precipitating Factors in Venous Thrombosis, Surg., Gynec. & Obst. **98**: 96, 1954.
37. Payne, J. T.: Indications for Ligation of the Inferior Vena Cava in Venous Thrombosis, A. M. A. Arch. Surg. **67**: 902, 1953.
38. Poer, D. H.: Discussion, Ann. Surg. **135**: 687, 1952.
39. Pratt, G. H.: Cardiovascular Surgery, Philadelphia, 1954, Lea & Febiger.
40. Pualwan, F., Jones, G. E., Bruny, S. J. A., and Dale, W. A.: Effects of Ligation of the Inferior Vena Cava With Absorbable Ligature, Surg. Forum, 40th Clin. Congress, Am. Coll. Surgeons, Philadelphia, 1955, W. B. Saunders Company, p. 179.
41. Ravdin, I. S., and Kirby, C. K.: Experiences With Ligation and Heparin in Thromboembolic Disease, SURGERY **29**: 334, 1951.
42. Ray, C. T., and Burch, G.: Vascular Responses in Man to Ligation of the Inferior Vena Cava, Arch. Int. Med. **80**: 587, 1947.
43. Robinson, L. S.: Vena Cava Ligation, SURGERY **25**: 329, 1949.
44. Scott, W. J. M., and Radakovich, M.: Venous and Lymphatic Stasis in the Lower Extremities, SURGERY **26**: 870, 1949.
45. Shea, P. C., and Robertson, R. L.: Late Sequelae of Inferior Vena Cava Ligation, Surg., Gynec. & Obst. **93**: 153, 1951.
46. Surington, C. T., and Jonas, A. F.: Intra-abdominal Venography Following Inferior Vena Cava Ligation, A. M. A. Arch. Surg. **65**: 605, 1952.
47. Thebaut, B. R., and Ward, C. S.: Caval Ligation, Surg., Gynec. & Obst. **84**: 385, 1947.
48. Veal, J. R.: Vena Caval Ligation (discussion), Ann. Surg. **135**: 686, 1952.
49. Veal, J. R., Dugan, T. J., Jamison, W. C., and Baversfeld, R. S.: Acute Massive Venous Occlusion of the Lower Extremities, SURGERY **29**: 355, 1951.
50. Veal, J. R., Hussey, H. H., and Barnes, E.: Ligation of the Inferior Vena Cava in Thrombosis of the Deep Veins of the Lower Extremities, Surg., Gynec. & Obst. **84**: 605, 1947.
51. Zollinger, R., and Teachnor, W. H.: Late Results of Inferior Vena Caval Ligations, A. M. A. Arch. Surg. **65**: 31, 1952.

DISCUSSION

DR. JOHN J. CRANLEY (Cincinnati, Ohio).—I support Dr. Dale's thesis that symptoms in the leg following vena cava ligation may be minimized. During a 5-year period we have ligated the venae cavae of 13 patients. One had a malignant lymphoma and died a few months postoperatively. One patient had repeated bouts of thrombophlebitis over a period of several years. He is the only patient to develop an ulceration of the leg. The remaining patients are fully rehabilitated and comfortable. All of our patients have been treated with elevation immediately postoperatively, and by that we mean elevation of the legs above heart level. All have had anticoagulant therapy for several weeks postoperatively and all have worn heavy-weight elastic stockings as long as any trace of ankle edema remained.

(Slide.) This recent picture shows the normal-appearing extremities of the first patient in this series whose vena cava was ligated in 1952. It is also representative of the other patients, with the exception of the one with recurrent thrombophlebitis. Like Dr. Dale, we are convinced on the basis of personal experience that most of the reported difficulties with the legs following vena cava ligation can be prevented by meticulous postoperative management.

DR. EDWARD A. EDWARDS (Boston, Mass.).—I think the renal veins are important in planning vena caval ligation. The left renal vein may descend obliquely to join the cava just above the iliacs, while the kidney may be in a normal position. For that reason the ligature should be placed close to the confluence of the iliac veins. Before performing caval ligation one should collect as much data on the patient as possible to determine where the kidneys are located to avoid ligating above the entrance of the vein of an iliac or pelvic kidney. The ovarian vein sometimes transmits emboli large enough to be lethal. For this reason one should think of performing transperitoneal ligation of both ovarian veins along with the cava in a multiparous patient. I believe anticoagulants are the single most important treatment in the prevention of postligation venous stasis.

DR. R. A. NABATOFF (New York, N. Y.).—We found a number of years ago that common femoral vein ligation above the insertion of the saphenous and superficial femoral veins is an extremely poor area in which to perform a ligation. Many of the sequelae occurred 3 to 4 years later. Some patients did not have any edema for 2 to 3 years and then edema, eczema, brownish pigmentation and ulceration would develop. About 66 per cent of the patients with common femoral vein ligation developed these sequelae. In doing a control study we found that many patients without any vein ligation also had sequelae after severe thrombophlebitis, indicating the need for anticoagulants, whether or not a vein ligation is performed. Immediate ambulation was practiced to prevent sequelae following vena cava ligation which is certainly preferable to common femoral vein ligation, as far as the prevention of sequelae and pulmonary emboli are concerned.

DR. EUGENE A. OSIUS (Detroit, Mich.).—We feel vena cava ligation is a life-saving procedure, but we also believe that the indication should be sharply defined and strictly adhered to. In spite of the fact that many patients do well after vena cava ligations, it is a known fact that there is considerable morbidity from the standpoint of ulceration, edema, and disability, and this must be weighed carefully against the benefits to be obtained. Among other things to be considered is the patient's status in life, as well as his occupation and his general activities. We do feel, however, with the author, that there is a very definite place for vena cava ligations and agree with his general tenets.

One other subject interested us, and that was Dr. Dale's reference to one patient developing a thrombosis after a long automobile ride on the thruway in New York. We believe this is a definite entity and have cautioned many of our patients for many years who have some disability not to drive or ride great distances without getting out of the car, moving about, and activating their limbs. We have had 4 or 5 cases of thrombosis, often in older individuals, but not exclusively so, following long airplane rides, usually transcontinental, where passengers could not get up and move about and were confined to a relatively small space in a bucket seat, and because of this they developed a thrombosis. We believe this is an entity worth watching for, and one which should be brought to the attention of the airlines industry, which I feel would be of definite benefit for both passenger and carrier.

DR. W. ANDREW DALE (closing).—The text of the paper summarized the important work of Dr. Edwards, and I am sure we should all be aware of these anomalies. I would like to make one further point. We previously published a paper on catgut ligation of the inferior vena cava in dogs[12] and have applied this in a few of the patients. We have not yet made any final determinations as to what happens after several months and do not wish to imply that we no longer use silk ligations, because ordinarily we do, and reserve catgut ligations as a clinical experiment for selected cases.

FEMORAL ARTERIOGRAPHY BY THE MOVING BAND RADIATION TECHNIQUE

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FEMORAL arteriography is the most valuable modality available for evaluating patients with peripheral vascular diseases who are suspected of lesions which might be amenable to direct surgical treatment. It is imperative that the maximum amount of information relative to the arterial system in the leg be obtained by a method of x-ray visualization in order to select cases suitable for surgical treatment. The location and extent of the occlusion must be well visualized. "Skipped" areas of arteriosclerosis obliterans must be noted. The status of the arterial system distal to the occluded segment must be ascertained and the presence of diffuse arteriosclerosis must not be overlooked. Femoral arteriography by the moving band radiation technique, reported by Astle and Jones,[1] has been very satisfactory in providing a maximum amount of information. This report presents an experience in using this technique with slight modification.

In the moving band radiation technique, the x-ray beam follows the opaque medium down the leg, thus assuring good arterial filling at the time of the exposure and uniform x-ray visualization. With this technique there is marked absence of the stray radiation which is associated with the multiple exposure arteriogram. This safety measure is important for the frequent operator. The technique is simple enough so that it can be done with the usual x-ray equipment in a general hospital. The technique can be standardized so that an infrequent operator will obtain consistently good arteriograms without the need for repeated injections of opaque medium with attendant danger of arterial thrombosis, systemic reaction to the medium, and a prolongation of the procedure.

TECHNIQUE

The principal features of the technique are long exposure and a narrow band of radiation which is moved slowly down the length of the leg to expose the entire major arterial system on a long 14 by 36 inch cassette. The standard cone with a length of 10 inches is used and covered by a lead diaphragm in which there is a rectangular slit 3 by ⅛ inch (Fig. 1). At a focal distance of 30 inches, the narrow band of radiation measuring 9 by ⅜ inch exposes an 8 inch wide band of the film. The cone is placed in the tube carriage so that

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the rectangular slit in the lead diaphragm is at right angles to the long axis of the leg. The slit is centered over the mid-portion of the leg and maintained at a focus-film distance of 30 inches.

The speed of the tube stand is timed by 3 markers placed next to the tube stand track. The first marker is opposite the upper end of the cassette, the second opposite the knee joint, and another marker opposite the ankle joint. The time markers enable the person operating the crank of the winch to regulate the speed of the tube stand in its course from the anterior superior iliac spine to the knee and between the knee and the ankle joint. The timing is accurately noted with a stop watch and the seconds are counted by one of the team during the entire travel of the tube stand. The crank of the winch has been operated manually because no automatic device has been found which is as satisfactory.

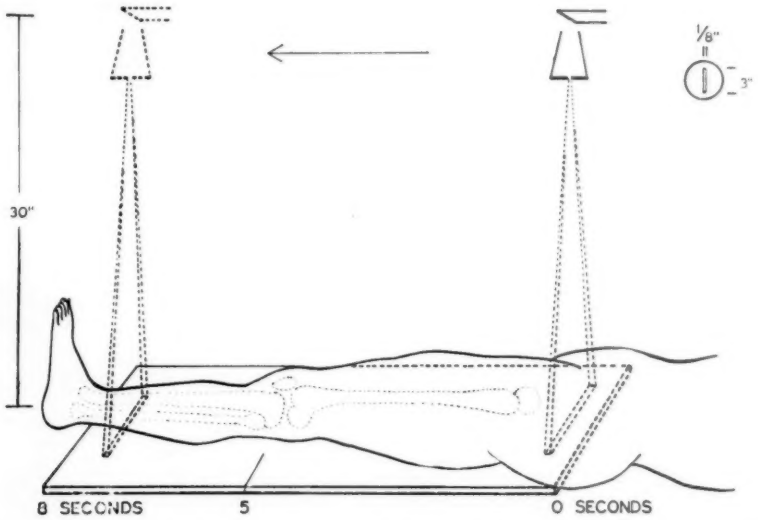

Fig. 1.—Diagram showing technical aspects of femoral arteriography by the moving band radiation technique.

For a leg of average thickness, it has been found that if the x-ray tube is moved from the anterior superior iliac spine to the knee in 5 seconds, and from the knee to the ankle in 3 seconds, the density of the film for the entire leg is excellent (Fig. 1). If the thickness of a part of the extremity is less than average, the speed of the tube stand should be increased; while if more than average, the speed of the tube stand should be decreased. The x-ray exposure factors are constant for all patients: 80 KVP, 25 MA, 10 seconds, and 30-inch focus-film distance.

The opaque medium used has been 30 c.c. of 50 per cent Hypaque sodium. This is injected into the common femoral artery just below the inguinal ligament via a 2-inch 18T needle introduced percutaneously. The injection is made within 5 seconds without any undue pressure, unless one wishes to obtain a retrograde filling of the iliac artery. The exposure is begun after 10 c.c. of the Hypaque sodium has been injected. The x-ray tube is placed at least 12 inches cephalad to

the anterior superior iliac spine. When the operator begins the injection of the opaque medium the tube stand is moved by the manually operated winch toward the foot of the patient. The x-ray exposure is started just before the x-ray tube reaches the anterior superior iliac spine and the exposure is continued over the entire length of the leg. The band of radiation virtually follows the opaque medium down the leg assuring good arterial filling at the time of the x-ray exposure and a uniform density of the arteriogram results.

Cooperation between surgeon, radiologist, and x-ray technician is of prime importance for a successful examination. A review of the sequence of events by individuals involved should be done before the actual examination in order to assure accurate timing of each step in the procedure.

DISCUSSION

Femoral arteriography by the moving band radiation technique for whole limb x-ray has provided a standard procedure for a variety of lesions affecting the arterial circulation in the leg. With no appreciable variations in the technique, one can predict a uniformly clear visualization of the entire arterial system. By this method one can correlate the arteriogram and the clinical findings with greater confidence in cases of thrombosis of femoral and popliteal arteries (Figs. 2 and 3), embolic occlusion of the popliteal artery (Fig. 4), and traumatic injuries to the arterial system (Figs. 5 and 6).

Thrombosis of femoral and popliteal arteries secondary to arteriosclerosis are lesions for which direct surgical procedures may be employed in carefully selected cases. To select proper patients for arterial grafting or thromboendarterectomy, a complete visualization of the arterial system of the leg must be obtained to avoid futile surgery. The status of the arterial system distal to the occluded segment is a principal concern in selecting patients for surgery. The arteriogram shown in Fig. 2 suggests an ideal situation for bypass graft. The distal arteries are well visualized and there are no "skipped" areas of stenosis or occlusion. This arteriogram can be contrasted with the arteriogram in Fig. 3 in which the popliteal artery distal to the thrombosed segment appears satisfactory, but the branches of the popliteal artery show numerous areas of stenosis and complete occlusion. This situation is unfavorable for direct femoral artery surgery because the blood flow distal to the thrombosed femoral artery is impeded sufficiently to cause postoperative thrombosis in the grafted segment or the segment treated by thromboendarterectomy.

The uniform clarity and reliability of the femoral arteriograms by the moving band radiation technique at any site in the arterial system is of considerable help in distinguishing between embolic occlusion and thrombosis secondary to arteriosclerosis. The arteriogram (Fig. 4) shows an embolic occlusion which occurred 5 years after a coronary thrombosis. It was manifested by intermittent claudication of the calf for 10 days prior to the arteriogram. Arteriotomy with embolectomy was the treatment of choice and the outcome was successful. At operation there was no gross arterial disease in

the popliteal artery and no attachment of the thrombus to the intima of the artery. In this instance both bypass graft and thromboendarterectomy were contraindicated.

A. *B.* Fig. 3.

Fig. 2.

Fig. 2.—Preoperative and postoperative femoral arteriograms. *A*, Preoperative shows occluded superficial femoral artery with excellent distal arteries. *B*, Postoperative taken 6 months after insertion of bypass homograft.

Fig. 3.—Bilateral arteriograms show thrombosis of superficial femoral arteries with numerous "skipped" areas of stenosis and complete occlusion in branches of the popliteal arteries.

Femoral arteriography may be of considerable help in recent and older injuries to arteries of the lower extremity. However, it is essential that the technique produce reliable visualization of the arterial system. One must be

able to accept with confidence that an artery is occluded which cannot be visualized. The arteriogram (Fig. 5) was taken 2 days after a compound fracture of the femur was sustained when it was apparent to the attending

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Section of whole limb arteriogram which shows embolic occlusion of popliteal artery which had occurred 10 days prior to arteriogram.

Fig. 5.—Whole limb arteriogram shows transected femoral artery at site of fractured femur. Complete thrombosis of distal arterial system is apparent.

Fig. 6.—Section of whole limb arteriogram shows occlusion of anterior tibial artery at site of fractured fibula from injury which had occurred 15 minutes prior to arteriogram.

physician that there was an associated circulatory impairment. The arteriogram shows the transected femoral artery and a complete thrombosis of the distal arterial system. Thigh amputation was inevitable. The arteriogram

(Fig. 6) was taken 15 months after fractures of the tibia and fibula were sustained at which time the patient complained of coldness and claudication in the left foot and inability to work. There was a medicolegal issue involved in this case as various consultants suggested the patient had had an associated arterial injury, a posttraumatic vasomotor disturbance, or had been malingering. The occlusion of the anterior tibial artery at the site of the fibula fracture (Fig. 6) established the cause for the symptoms in the left foot.

SUMMARY

Femoral arteriography by the moving band radiation technique has been an entirely satisfactory method for obtaining a whole limb visualization of the arterial system. The advantages are simplicity, uniform density and visualization of the arteries, marked absence of stray radiation, avoidance of repeated injections, and the exact measurable delineation of arterial defect.

The more complete visualization of the arterial system distal to an occluded segment has resulted in a better selection of patients for direct arterial surgery. The method is a reliable technique for evaluating recent and late arterial injuries of the legs as well as for differentiating between embolic and thrombotic occlusions.

REFERENCES

1. Astle, W. E. C., and Jones, D. Wallace: A Simple Radiological Technique for Femoral Angiography, Brit. J. Radiol. **26**: 658-659, 1953.
2. Morton, S. A., and Byrne, R. W.: Scanographic Method for the Visualization of the Blood Vessels, Radiology **69**: 63-69, 1957.

Discussion

DR. E. STANLEY CRAWFORD (Houston, Tex.).—I was impressed by the beautiful arteriograms obtained by the method under discussion. We have explored the use of this technique and although satisfactory arteriograms were obtained in most instances, several disadvantages became apparent that caused us to abandon its use in the routine case. In the first place an average exposure time of 6 to 8 seconds for each arteriogram on a busy vascular service is potentially dangerous to the operator despite reasonable shielding and, second, the technique does not eliminate the element of estimation of collateral blood flow.

Similar arteriograms may be obtained more safely by 2 brief exposures of less than one-half second each using a 36-inch cassette and a specially constructed tunnel. The cassette occupies the lower section of the tunnel and a movable 14 by 18 inch steel plate occupies the upper section of the tunnel. The patient is placed upon this device and exposable film extends from the iliac crest to the ankle. As the last cubic centimeter of contrast media is injected, the first exposure is made of the thigh from a distance of 54 inches following which the steel plate is pulled cephalad to shield the thigh area and permit exposure of the lower leg. The second exposure is made from 4 to 8 seconds after the first and is estimated on the basis of the collateral blood flow. Aortofemorogram may be obtained by employing the same equipment. Exposure time has been significantly reduced by this technique and individual variation of the technique is permitted.

DR. NORMAN E. FREEMAN (San Francisco, Calif.).—Any technique which can be developed to visualize the blood vessels and, at the same time, protect the patient is valuable. I should like also to emphasize the importance of protecting the individual who is doing the arterial injection. I have been somewhat disturbed about the amount of exposure to

which we as vascular surgeons subject ourselves. The use of lead gloves does not seen to be the answer because these are too cumbersome. We have attempted to use a lead shield on a swivel. This device may be of help.

One other point is the type of solution. Recently Dr. Leeds and I have used 76 per cent Renografin under local anesthesia. We have avoided general anesthesia entirely. In the last 200 cases we have had no serious consequences. Occasionally there is extravasation, which is painful but not dangerous. For aortography we have also used 85 per cent Renografin. For peripheral arteriograms, 50 per cent Hypaque has been used and we consider it much better as far as the patient is concerned.

DR. JAMES E. CONLEY (Closing).—I should like to comment upon the opaque medium used. We have used 50 per cent sodium Hypaque for all of our femoral arteriograms.

The 90 per cent sodium Hypaque mentioned by Dr. Freeman has been tried by us for translumbar aortograms but the solution is too viscus to inject rapidly, so we have continued to use 75 per cent Neo-Iopax.

PROTECTIVE EFFECT OF INTRA-AORTIC INJECTION OF PROCAINE AGAINST RENAL INJURIES PRODUCED IN EXPERIMENTAL AORTOGRAPHY

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THE various complications of translumbar aortography have been reviewed recently by McAfee and Willson[4] and by Crawford, Beall, Moyer, and DeBakey.[1] Pain or hemorrhage occurs infrequently and relates to technique of puncture of the aorta or to its disease. Occasionally, difficulties have occurred because of anesthesia. Also, systemic allergic reactions may occur after the iodinized contrast media. To minimize this, small preliminary test doses usually are recommended before aortography as employed before urography. More serious complications of aortography are injury to the kidney, the spinal cord, or the bowel. Likelihood of injury to the kidney or the bowel increases when the needle used for aortic puncture is improperly placed and directs the contrast media into a renal or a mesenteric artery. Tarazi, Margolis, and Grimson[5] demonstrated in dogs that the chances of injury to the spinal cord markedly increase if the supine position is used. Most patients are turned to a prone position for aortography. Aberrant locations of the larger spinal arteries were also described as an explanation of injury of the spinal cord.

Injury of the kidneys, spinal cord, or bowel apparently is caused by the perfusion of the organ with an inadequately diluted solution of the contrast media. This is more likely to occur when the media are injected near a branch of the aorta or if an obstruction exists as in patients with the Leriche syndrome. It can occur in an unobstructed and free flowing aorta if a large enough volume of a highly concentrated solution is injected rapidly. Because of this risk, the current practice of most groups doing aortography has been to use smaller amounts and more dilute solutions of contrast media and to make a check of the position of the point of the needle by an x-ray after a preliminary injection of 5 c.c. of the media.

Our previous studies, Tarazi, Margolis, and Grimson[5] and Thomson, Margolis, Grimson, and Taylor,[6] described experimental injury of the spinal cord and of the kidneys and emphasized that there is a difference of toxicity of equal concentrations of 4 contrast media studied. Urokon sodium and Diodrast were the most toxic, Miokon and Hypaque the least. These studies also

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developed techniques whereby the lesions could be produced consistently. The plan of the present experiment was to use these techniques to explore the possibility that the injection of a drug into the aorta, prior to the injection of a contrast media, might minimize damage.

METHOD

Urokon sodium* was selected as the standard contrast medium. A double lumen catheter, 30 inches in length, was designed for introduction upward through a femoral artery into the aorta. Its outside diameter was 8 F. One lumen, 4 F. in diameter, was connected to 2 balloons 4 inches apart at the end of the catheter. The balloons were large enough to obstruct the aorta above and below the origin of the renal arteries when inflated. The second lumen, 5 F. in diameter, terminated at an opening midway between the 2 balloons. This was arranged so that injection of a drug or a contrast media would be near the origin of each renal artery. Dogs weighing 10 to 36 kilograms, usually around 20 kilograms, were anesthetized using sodium Nembutal, 30 mg. per kilogram. The double lumen catheter was then passed up the left femoral artery until the injection orifice lay near the renal arteries. The left carotid artery was then divided and the proximal end cannulated so that mean systolic blood pressure could be recorded continuously on a kymograph. Respirations were also recorded. Each animal was then placed on its left side with its back against a vertical x-ray table so that the trunk of the dog could be exposed to roentgen rays delivered horizontally and recorded on a film. Intra-aortic injections of the contrast media and of the drug to be tested for prophylactic value were made through the 5 F. lumen during 2 or 3 seconds using maximum manual force on a 30 or 50 c.c. syringe. When a test drug was administered, it was injected through the same 5 F. lumen, 30 to 90 seconds before the Urokon.

When the animals were prepared in the left lateral position with the catheter in place and with the blood pressure recording, the 2 balloons were inflated by injecting air through the 4 F. lumen. This caused a temporary increase of blood pressure (Fig. 1). After a minute or more the pressure usually leveled off to a moderate elevation. The test drug was then injected and another rise usually occurred. Thirty to 90 seconds later the Urokon was injected. The Urokon ordinarily caused the greatest increase of pressure. After a minute or more, and when the pressure elevation had stabilized, the balloons were deflated.

A roentgenogram (Fig. 2) was obtained just before completing the injection of the Urokon. This roentgenogram was used to prove the position of the balloons and the trapping of contrast media or its infusion through the renal arteries. Three animals were excluded from the series because of improper position of the catheter, another because there was no evidence of contrast media between the balloons or in the kidneys.

Ten preliminary experiments, also not included in the series, were performed to test the catheter and to determine the optimum dose of Urokon.

*Supplied by Mallinckrodt Chemical Works, St. Louis, Mo.

Urokon, 70 per cent, in amounts of 0.5, 1.0, 1.5, and 2.0 c.c. per kilogram of body weight were given as a single injection. The animals were sacrificed 4 days afterward. Minor injury to the kidneys occurred after 0.5 c.c./Kg.; severe necrosis occurred after 1.5 and 2.0 c.c./Kg. The optimum toxic dose seemed to be 1.0 c.c./Kg. Thereafter, all experiments were performed using 70 per cent Urokon sodium, 1.0 c.c./Kg. of body weight. The double lumen,

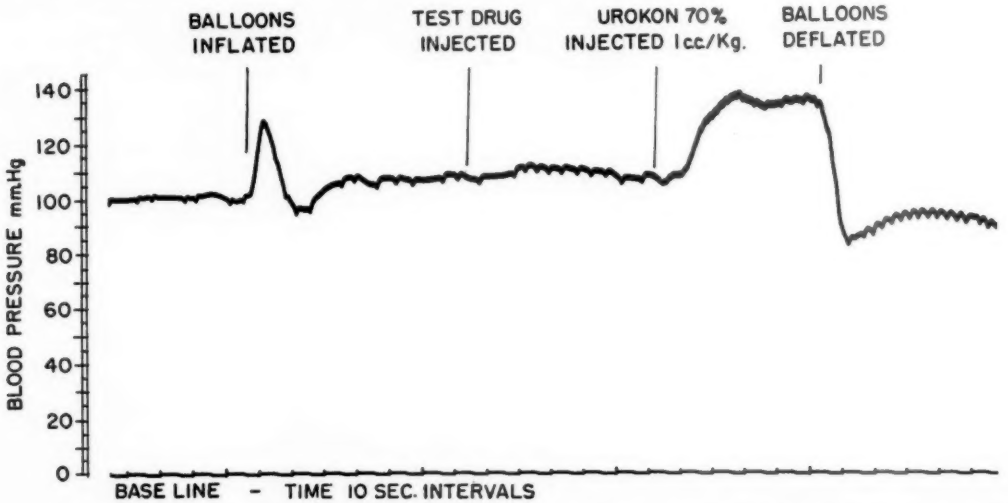

Fig. 1.—The kymograph tracing shows the typical response of blood pressure as the intra-aortic balloons were inflated and subsequently deflated. During the period of occlusion of the aorta, a drug to be tested for prophylactic value was injected 30 to 90 seconds before the toxic dose of 70 per cent Urokon sodium.

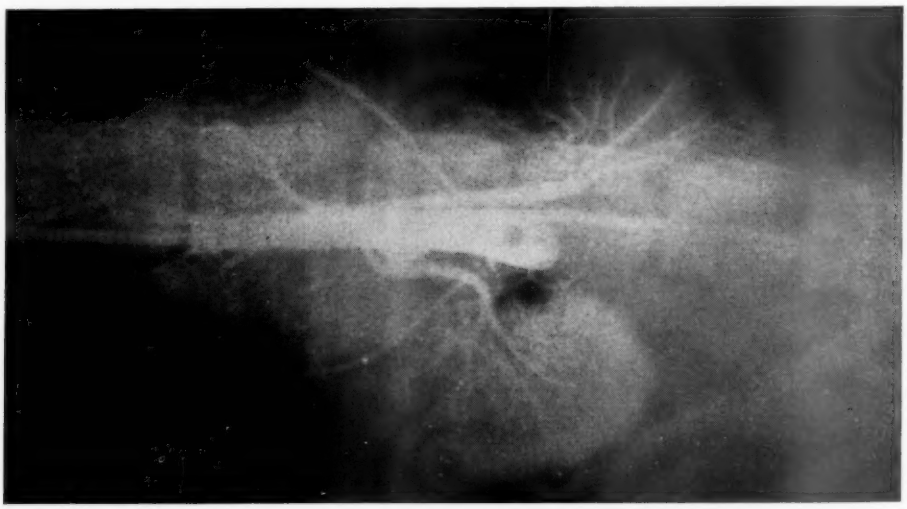

Fig. 2.—The roentgenogram shows the contrast media trapped between the 2 balloons of the intra-aortic catheter and perfusing the renal arteries. The density of the inferior kidney is somewhat greater than that of the superior kidney.

double balloon catheter seemed to localize the Urokon in the region of the renal arteries, to produce renal damage consistently with the dogs in a lateral position, and yet to minimize the incidence and severity of the spinal convulsions which would otherwise occur with this dose.

The drugs for intra-aortic injection prior to the Urokon were selected arbitrarily. The drugs, doses, and volumes were: Priscoline 1 mg./Kg. (20 c.c.), Nupercaine 0.825 mg./Kg. (15 to 24 c.c.), Chlor-Trimeton 0.5 mg./Kg. (10 c.c.), glucose 0.5 Gm./Kg. (35 to 59 c.c.), Vasoxyl 0.025 mg./Kg. (20 c.c.), and procaine 25 mg./Kg. (21 to 36 c.c.). In another experiment, 2 per cent procaine, 25 mg./Kg., was mixed with Urokon, 1.0 c.c./Kg., and given as a single injection in a volume which varied from 34 to 54 c.c.

A total of 53 dogs divided into 8 groups or types of experiment were used in this study. Seven dogs received Urokon alone. Groups of 6 to 9 dogs each received one of the test drugs 30 to 90 seconds before the Urokon. A group of 6 dogs was used for a mixture of Urokon and procaine which was given as a single injection.

RESULTS

Blood Pressure.—All animals were at normotensive levels before the intra-aortic balloons were inflated. An abrupt transient increase of mean systolic blood pressure occurred with inflation of the balloons. The average sustained rise during the next minute or two and before any injection averaged 18 mm. Hg for the 53 dogs and ranged from 2 to 36 mm. In the group of dogs receiving Urokon alone there was an increase of blood pressure with the Urokon, averaging 66 mm. and ranging from 22 to 118 mm. This was sustained during the next 1 or 2 minutes after which time the balloons were deflated. In the experiments testing a drug for prophylactic value, an increase of pressure occurred with the administration of the drug, between the rise with the occlusion of the aorta and the rise with injection of Urokon. In the Priscoline group, the average increase was 22 mm. Hg above the occlusion pressure and there was an additional or final rise averaging 62 mm. Hg when the Urokon was given. With Nupercaine there was an average rise of 2 mm. followed by another of 30 mm. with the Urokon. With Chlor-Trimeton the average increases were 6 and 62 mm. With glucose they were 6 and 26 mm. With Vasoxyl they were 14 and 96 mm. With procaine they were 2 and 40 mm. With the group receiving procaine and Urokon mixed and injected at once, the average rise of blood pressure above the level of occlusion of the balloons was 44 mm. Hg.

Examination of the changes of pressure with Urokon for the individual dogs in each of the 8 groups indicated that there was no relationship between the rise of pressure and the subsequent damage to the kidneys in the animals receiving Urokon alone or Vasoxyl before Urokon. For the individual dogs of the remaining 6 groups, there seemed to be a little more damage to the kidneys among the animals whose pressure rose the highest.

Re-examination of the group averages of the increase of blood pressure with the Urokon for each of the 6 groups receiving prophylactic test drugs shows that the Priscoline, Chlor-Trimeton and Vasoxyl groups were followed by average increases of pressure of 62, 62, and 96 mm. Hg, respectively, an increase equal to or above the 66 mm. Hg average of the group given Urokon alone. The glucose, Nupercaine, and procaine groups were followed by average increases of 26, 30, and 40 mm. Hg, respectively, with Urokon, rises less

than the 66 mm. average of the group of dogs receiving Urokon alone. This would place glucose, Nupercaine, and procaine together as the more favorable drugs from the point of view of avoiding increases of pressure.

Paralysis.—The catheter technique, using balloons to occlude the aorta above and below the renal arteries, markedly reduced the incidence of spinal convulsions and subsequent paralysis which otherwise would be expected with 1 c.c. of Urokon per kilogram of body weight. However, occasional animals did develop these complications. Of the 7 dogs receiving Urokon alone, 4 had convulsions and paralysis. Of the group of 6 receiving Priscoline, one developed these complications. Of the 6 dogs in each of the groups receiving Nupercaine, glucose, or Chlor-Trimeton and of the 9 receiving procaine, 27 dogs altogether, no animal developed spinal convulsions or paralysis. From this point of view, these 4 drugs looked favorable. Of the 6 dogs receiving procaine and Urokon in a single injection, no dog developed convulsions or paralysis. Since the 70 per cent Urokon had been diluted to approximately a 30 per cent concentration by the procaine solution, it cannot be determined whether the procaine mixture afforded any protection.

Roentgenograms.—The films of the 53 dogs which were included in the series have been reviewed to determine that the injection had been near the origin of the renal arteries. Also, they have been reviewed to determine whether there was any difference of density of the kidney which had been in the superior position at the time of injection as compared to that which had been dependent. Forty-six films demonstrated well the aorta, the renal arteries, or both. Seven films were technically less satisfactory because of improper or double exposure or faulty developing. These 7 animals were included in the series because the films seemed to give some information and since the experiments were otherwise satisfactory. Of the 53 dogs, both the renal arteries and the kidneys were well visualized in 31 animals. The aorta was well visualized with contrast media trapped between the balloons in 34. Since a rapid film changer was not used, it was not possible to record the aortic and the renal phase of perfusion for each animal.

Of the 31 animals whose x-rays were satisfactory for comparing the density of the superior and the dependent kidneys, the dependent kidney seemed more dense than the superior kidney in 25.

Histopathologic Examinations.—Each of the 53 dogs were sacrificed 3 or 4 days after the injection of 70 per cent Urokon sodium. The kidneys were removed and submitted to one of us (G. M.). He interpreted the microscopic findings without knowing whether the Urokon had been injected alone, following a test drug or mixed with procaine. The degree of injury in each kidney was graded according to our previously described classification.[6] This classification had 5 categories. The first two were "no lesions" and "nephrosis, slight." These two categories were defined as having no renal lesions attributable to the contrast agent or a mild focal tubular injury which was not quantitatively significant in extent. In the interest of simplifying this report, these two categories have been grouped together and all kidneys in

these groups were considered as having no signficant lesions. The third category, "nephrosis, moderate," included those kidneys having incomplete but quantitatively significant tubular involvement throughout or over the distribution of a major branch of the renal artery (Fig. 3, *A*). The fourth, "nephrosis, severe," included those showing an advanced tubular injury affecting all or virtually all nephrons throughout the kidney or over the distribution of a major extrarenal branch of the renal artery (Fig. 3, *B*). The fifth category, "cortical necrosis," included those with a necrotizing effect involving all tissue elements, glomeruli as well as tubules, affecting primarily the outer cortex but sometimes extending into the medulla (Fig. 3, *C*). These third, fourth, and fifth categories are described in this report by name, nephrosis moderate, nephrosis severe, and cortical necrosis. In the interest of further simplifying the present report the lesions of the 2 kidneys of each dog when different have been assigned the classification most representative of the intensity of injury for that dog. The details of the histopathologic study, microscopic and gross, will be the subject of a subsequent report by one of us (G. M.).

The simplified classification and representation of the severity of the lesions in individual dogs is shown in Table I. It is evident that no animal receiving Urokon alone or Urokon after Priscoline failed to have significant renal injury. Also, marked increases of blood pressure or paralysis developed in several dogs of these groups. Two animals each in the Nupercaine and Chlor-Trimeton groups and 3 in the glucose group had no significant lesion. Marked increase of blood pressure and paralysis did not occur in these 3 groups. Although 5 of the 7 animals who received Vasoxyl before Urokon had no lesion of the kidney, several dogs of this group developed increase of blood pressure or occurrence of spinal convulsions and paralysis. Seven of the 9 dogs treated with procaine before Urokon had no significant lesion. Also there was no paralysis in the procaine group and the rise of pressure was less than that expected after Urokon alone. Where procaine and Urokon were given together

TABLE I. HISTOPATHOLOGIC FINDINGS IN KIDNEYS (FIGURES = NUMBER OF DOGS)

	WITHOUT LESION	WITH LESION	SEVERITY OF LESIONS		
			NEPHROSIS MODERATE	NEPHROSIS SEVERE	CORTICAL NECROSIS
Urokon alone*	0 of 7	7	3	4	0
Urokon after					
Priscoline*	0 of 6	6	4	2	0
Nupercaine	2 of 6	4	2	1	1
Chlor-Trimeton	2 of 6	4	1	2	1
Glucose	3 of 6	3	1	2	0
Vasoxyl*	5 of 7	2	2	0	0
Procaine	7 of 9	2	1	0	1
Injection of mixture					
Procaine and Urokon	3 of 6	3	1	1	1

*Increased pressure and caused paralysis.

The results in the 53 dogs given toxic doses of Urokon sodium alone, 30 to 90 seconds after a drug tested for prophylactic value or diluted with procaine, are presented. The greatest protection occurred when the Urokon had been given 30 to 90 seconds after procaine.

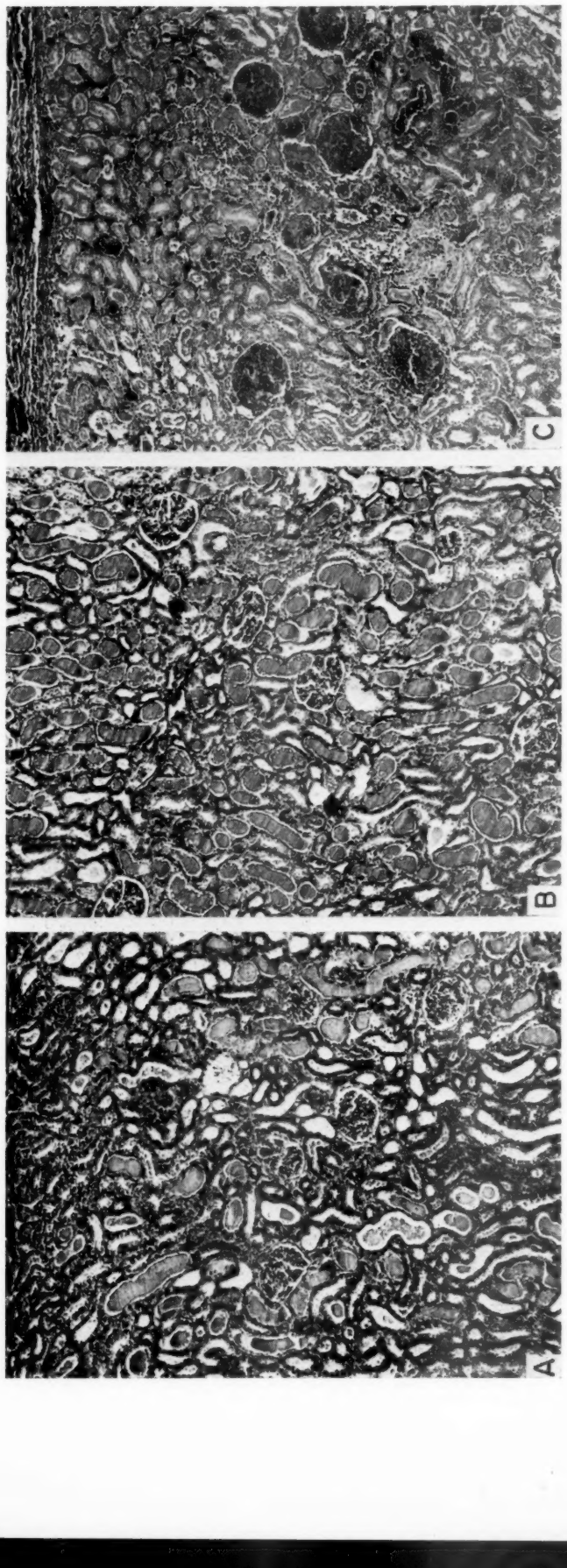

Fig. 3.—Typical sections of kidney, 4 days after intra-aortic injection of toxic doses of Urokon sodium, illustrate (*A*) moderate necrosis, (*B*) severe necrosis, and (*C*) these plus cortical necrosis.

as a single injection with the Urokon diluted to about 30 per cent, 3 of 6 dogs had no significant lesion. The results with procaine given 30 to 90 seconds before Urokon were the most favorable of these groups.

The severity of the lesions which did occur in the 8 groups is presented in Table I. Moderate and severe nephrosis occurred most frequently; cortical necrosis occurred least frequently.

The damage of the dependent kidney relative to that of the superior kidney was examined for each dog of each group. The superior kidney was the more severely damaged in the groups given Urokon alone or Urokon after glucose. With Chlor-Trimeton and Nupercaine, there was no difference. The dependent kidney was more severely damaged in the Priscoline, Vasoxyl, and procaine groups. Of the entire 53 animals, all groups considered together, the dependent kidney was more severely damaged in 15, the superior in 8, and the damage was equal in 10. There was no renal damage in 20.

DISCUSSION

The experiments were designed to determine whether the intra-aortic injection of a drug 30 to 90 seconds before Urokon sodium could lessen the incidence or severity of injury to the kidneys. Although the intra-aortic balloons were inflated above and below the level of the renal arteries, some animals developed spinal convulsions and later exhibited paralysis. Of the drugs tested, procaine seemed to afford the greatest protection against renal and cord injury, Priscoline the least. The dosages of the test drugs used were selected arbitrarily and are not necessarily the most effective. The time interval between injection of the test drug and the contrast media also was set arbitrarily (30 to 90 seconds). This is not necessarily the optimum interval. However, results were better than in those experiments using simultaneous injection of procaine and Urokon.

Goodwin and Walter,[2] in 1953, reported the intra-aortic injection of small doses of procaine (30 to 60 mg.) just before the rapid injection of a contrast media during aortography in patients prepared by sedation and local anesthesia. This they believed did reduce pain. Procaine often has been used in femoral arteriography to lessen pain. We have confirmed lessening of pain in femoral arteriography, using 40 to 200 mg. of procaine a minute before Miokon or Hypaque. Goodwin and Walter[2] quote Graubard as stating that up to 40 mg. of procaine per kilogram of body weight could be given to patients intravenously without serious reaction. Our experience with patients has included 200 mg. per patient subcutaneously frequently and 200 mg. intra-aortically occasionally in anesthetized patients without adverse reaction. On the basis of the dose of 25 mg. per kilogram used in our experiments in dogs, a patient weighing 70 Kg. would need 1,750 mg. injected into the aorta to have an equal dose. However, the experiments employed toxic doses of contrast media trapped between balloons. Also, the minimum effective or optimum dose necessary for the dog was not determined. Man and dog often vary in drug requirements. Accordingly, it is not possible to recommend a dose from

these animal studies for use in man. Renal and spinal cord injuries occur infrequently in man. Aortography would have to be done in a series of several hundred patients to confirm the observation that procaine protects dogs against injury. At present it is our plan to use gradually increasing doses of procaine intra-aortically 30 to 90 seconds before a contrast media in patients, in the hope that a maximum well-tolerated and possibly effective dosage can be evolved.

Kenan, Tindall, Margolis, and Wood[3] in a concurrent study have tested Arfonad, Papaverine, heparin, varidase, glucose, procaine, and hypothermia as possible means of protecting the spinal cord against injury by Urokon sodium 70 per cent (1 c.c. per kilogram) injected intra-aortically through a retrograde catheter passed up the femoral artery of dogs. They found that only with hypothermia, procaine, and glucose was a significant protection obtained. They concluded that glucose (1 or 2 Gm. per kilogram of body weight) was the superior of these 3 therapeutic approaches, although procaine also had a remarkable protective effect.

Our experiments were not designed to explore the causes of the injury by contrast media or the mechanism of the protection. They do indicate that the prophylactic intra-aortic injection of procaine best minimized likelihood of renal damage; Vasoxyl, glucose, Chlor-Trimeton, or Nupercaine gave less protection. The associated observations on spinal convulsions and paralysis indicated that cord damage did not occur in the 4 groups of 6 to 9 dogs each receiving prophylactic intra-aortic injections of Nupercaine, glucose, Chlor-Trimeton, or procaine. These studies encouraged us to select procaine as the drug of preference for use during aortography to protect both the kidneys and the spinal cord. A time interval of 30 to 90 seconds between injection of the drug and of the contrast media seems important to success of protection. Only if it becomes well established that procaine protects patients would it be possible to return to larger doses of contrast media for better roentgenologic detail.

CONCLUSION

1. Intra-aortic injection of 70 per cent Urokon sodium (1 c.c. per kilogram) between balloons which obstruct the aorta above and below the origin of the renal arteries in dogs regularly causes moderate to severe nephrosis and often paralysis.

2. Intra-aortic injection of procaine (25 mg. per kilogram) 30 to 90 seconds before 70 per cent Urokon sodium with this technique in dogs usually prevented significant renal injury and did prevent paralysis.

3. Priscoline did not lessen the severity of the renal injury following Urokon. Nupercaine, Chlor-Trimeton, glucose, and Vasoxyl afforded less protection than procaine in the doses employed.

4. The incidence and the degree of injury of the dependent kidney were somewhat greater than that of the superior kidney.

REFERENCES

1. Crawford, E. S., Beall, A. C., Moyer, J. H., and DeBakey, M. E.: Complications of Aortography, SURGERY. In press, 1957.
2. Goodwin, W. E., and Walter, R. C.: Intra-Aortic Procaine Injection in Aortography, Angiology 4: 410, 1953.
3. Kenan, P. D., Tindall, G. T., Margolis, G., and Wood, R. S.: Prevention of Experimental Contrast Medium Injury to the Nervous System, J. Neurosurg.: In press, 1957.
4. McAfee, J. G., and Willson, J. K. V.: A Review of the Complications of Translumbar Aortography, Am. J. Roentgenol. 75: 956, 1956.
5. Tarazi, A. K., Margolis, G., and Grimson, K. S.: Spinal Cord Lesions Produced by Aortography in Dogs, A. M. A. Arch. Surg. 72: 38, 1956.
6. Thomson, H. S., Margolis, G., Grimson, K. S., and Taylor, H. M.: Effects of Intra-Arterial Injection of Iodine Contrast Media on the Kidney of the Dog, A. M. A. Arch. Surg. 74: 39, 1957.

DISCUSSION

DR. ELLIOTT S. HURWITT (New York, N. Y.).—Measures to minimize hazards such as those that have been presented are of the utmost importance. Since the intravenous route is anatomically so much safer than the intra-aortic or intracardiac, if the abdominal aorta could be visualized well by the intravenous route we would all welcome such a technique. Here are the abdominal aorta and iliac arteries visualized by an intravenous injection in the antecubital vein employing 50 c.c. of 70 per cent Urokon in a very obese patient with suspected aneurysm of the aorta. (Slide.) We feel that many of the hazards of direct aortography can be avoided by this technique. We have been able to visualize the entire abdominal aorta by this route.

DR. ROBERT SHAW (Boston, Mass.).—The serious complications of aortography are of concern to all of us, and this paper is a valuable contribution in that it suggests a means of reducing these complications. I think it would be worthwhile to emphasize one point in this regard. The objective of aortography is to obtain a sufficient concentration and amount of dye within the arteries to adequately visualize them. To inject an amount of dye greater than is necessary to accomplish this is dangerous and unnecessary. A patient with aortic occlusive disease will have a slowly flowing stream of blood in the aorta, and a decreased total volume of blood within the aorta and its branches, consequently, will require a smaller total dosage of dye and a slower rate of injection to accomplish adequate x-ray visualization. Failure to reduce the total dosage dye and the rate of injection in patients with aortic occlusive disease has led to unusually high dye concentrations in aortic blood and consequent toxic manifestations. This realization of the slow linear rate of flow of arterial blood in occlusive disease has led to considerable simplification in our technique of femoral arteriography. We find that we can adequately fill the entire arterial tree of the leg by injecting the usual dose of dye over a 5 or 6 second interval in femoral artery occlusive disease and thus avoid the necessity for cassette changers and multiple exposures.

DR. E. STANLEY CRAWFORD (Houston, Tex.).—Studies of this type which may lead to safer aortography are indeed extremely important. The total incidence of complication from aortography is small; however, the most frequent and serious disturbance seen after this maneuver is renal damage. Perhaps such studies as these will eventually provide an antidote to the harmful effect of the contrast media on the kidney. However, at the moment it must be remembered that the 2 most important factors in the production of renal injury are dosage of contrast media and site of injection. Direct renal artery injection invariably produces injury to the perfused kidney. Consequently the aorta should be pierced some distance from these vessels. The constant factor in the reported cases of bilateral renal injury has been large doses of organic iodides. Using detailed differential renal function studies, we have found significant reduction in glomerular filtration rates in 40 per cent of the cases when doses greater than 35 c.c. of 70 per cent Urokon sodium were employed. Renal function by such techniques has not been disturbed with doses less

than 35 c.c. and a case of renal damage using such small doses of organic iodides has not been reported. Very satisfactory studies may be obtained with this safe dose of 70 per cent Urokon sodium.

DR. J. C. LUKE (Montreal, Canada).—I would like to make a suggestion in respect to aortography. In those cases where the kidneys are well visualized and especially in such cases where a Leriche syndrome is present, I would suggest further x-ray pictures over the succeeding 24 to 48 hours. If later pictures show dye still remaining in the kidney, it indicates severe renal damage and one is forewarned of actual or potential renal shutdown. We have had 2 cases, one which showed both kidneys to retain the dye and one only the right. The first patient died of uremia on the sixth day and the latter recovered but with signs of extensive right kidney damage.

DR. KEITH S. GRIMSON (closing).—Certainly everything possible should be done to minimize the complications of aortography. Dr. Crawford's comments about reduction of volume to 30 c.c. or less are wise. However, our experiments indicate that the use of Urokon increases risk; Miokon or Hypaque was less toxic. Better detail would be obtained if we could go back to use of larger volumes and higher concentrations of iodine with safety. Although our studies do indicate that procaine injected 30 to 90 seconds before Urokon in dogs increased safety, this cannot be transposed immediately to man. More experimental work needs to be done. We have used 200 mg. through the aortic puncture needle in patients, but to equal the dose in dogs a patient weighing 70 kilograms might require 1,750 mg. We are using increasing doses of procaine a minute before contrast media in aortography to try to determine a maximum well-tolerated dose. Many aortograms must be done before it will be known whether procaine protects patients.

AN EXPERIMENTAL REVALUATION OF THE PROBLEM OF SMALL VESSEL REPLACEMENT

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INTRODUCTION

ONE of the major problems in vascular surgery today is that of small vessel replacement. In contrast to the excellent results obtained with resection and replacement of segments of aorta or iliacs, grafts or prostheses in the smaller peripheral vessels have shown a disturbingly high incidence of thrombosis. Attempts to improve results in the replacement of long segments of peripheral vessels have been more or less empirical and have fallen into 2 main categories. On the one hand various technical maneuvers have been tried such as oblique or Z-plastics to increase the diameter of end-to-end anastomoses, end-to-side anastomoses, and so forth. On the other hand replacement substances have been varied to include a great assortment of plastic materials.

An early study[8] of arterial homografts has been interpreted as showing that the success or failure of a graft is not influenced by its length. This experiment was performed on dog aortas. Although length of graft may be of minor importance in large vessels, a study[1] of long vascular grafts using the femoral and iliac arteries of dogs indicates that the same cannot be said for small vessel replacements. Nevertheless, much of the experimental work in this field has been performed with relatively short grafts and hardly applies to the clinical problem of long segment replacement as we see it today. In addition, with few exceptions, the duration of follow-up of arterial replacement substances used experimentally has been short, while, clinically, occlusions in small vessel grafts may not occur until many months after operation.

With these considerations in mind, preparations were made to study long small vessel grafts with relatively protracted periods of follow-up. Since previous work in our laboratory[10] had shown that the carotid arteries of the dog provided a rather critical proving ground for small vessel grafts, these vessels were chosen for the experiment.

For this study 3 types of arterial replacements were selected: fresh autogenous, freeze-dried autogenous, and freeze-dried homogenous grafts. Since aseptic technique was observed in obtaining and handling the freeze-dried grafts, no sterilizing agent was used in their processing. Assuming, and we believe

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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justifiably so, that if fresh autogenous grafts are inserted with proper technique few, if any, occlusions should result, we utilized these grafts as controls to evaluate the commonly employed method of end-to-end anastomosis. With type of anastomosis unchanged, freeze-dried autogenous grafts were then studied in order to determine the effect of processing and storage upon end results in these small vessel grafts. Finally, freeze-dried homogenous grafts were compared with the freeze-dried autogenous grafts to detect any differences in results which might be attributed to a specific effect of devitalized homogenous tissue. So far as we can determine, this utilization of the freeze-dried autograft as an intermediate control to separate the effect of processing and a specific tissue reaction has not been practiced before. The importance of determining the relative effects of each of the above variables on the success or failure of small vessel grafts in order to channel further studies in this field must be apparent.

MATERIALS AND METHODS

Adult mongrel dogs were used. Groups were necessarily small because of the expense and kennel space involved in a long-term experiment of this type. Enough grafts were inserted to reasonably assure that 10 or more of each type of graft would complete the study. Grafts were 10 cm. or greater in length. These were followed for one year or until such time as it was demonstrated that occlusion had occurred. Using sodium pentobarbital anesthesia and sterile technique, vessel segments were removed and grafts were introduced through short vertical incisions in the neck, high and low over the suture lines, the vessel being exposed and freed by tunneling between the incisions. The upper anastomosis in the carotid artery was just below its thyroid branch and the lower a few centimeters above the take-off from the brachiocephalic artery. Two continuous everting mattress sutures of 6-0 arterial silk were used for each anastomosis. At the conclusion of the operative procedure each dog received 1,500,000 units of penicillin and one gram of streptomycin intramuscularly.

Group I. Fresh Autogenous Grafts.—The segment of carotid artery was excised, cleared of excess adventitia in the same manner that vessel segments are prepared for freeze-drying, and then sutured back in place. Fourteen such procedures were performed.

Groups II and III. Freeze-dried Autogenous and Homogenous Grafts.—The operative procedure on the left carotid was the same as that for Group I, except that the segment removed was freeze-dried and the defect produced was bridged by a freeze-dried segment of carotid artery of corresponding length obtained from a previously operated dog (Group III, freeze-dried homografts).

Two weeks or more after operation upon the left, the right carotid was exposed, the proper length segment removed, and the freeze-dried segment from the left carotid introduced (Group II, freeze-dried autografts). The segment removed from the right carotid was freeze-dried to be used in a subsequent experimental animal as the homograft on the left. There were 12 freeze-dried autografts in Group II and 14 freeze-dried homografts in Group III.

RESULTS

Group I. Fresh Autografts.—The only significant infection in the entire experimental series accounted for an early failure (suture line disruption) of one of the fresh autografts. One animal suffered a fatal accident 3 days after insertion of the graft and another died of distemper on the twenty-fourth postoperative day. In both of these latter instances, the graft was patent and free of thrombosis. Eleven fresh autogenous grafts remained to be followed for the duration of the experiment (Table I). Two (18 per cent) of the 11 were occluded at the end of one year. The 9 patent grafts showed no significant constriction, thrombosis, or dilatation.

TABLE I. FRESH AUTOGRAFTS

DOG NUMBER	PERIOD OF FOLLOW-UP (MONTHS)	OUTSIDE DIAMETER OF GRAFT* (MM.)	LENGTH OF GRAFT* (CM.)	RESULT
1943	14		13	Patent
2046	14	3	12	Patent
1985	14		11	Patent
1960	14	3	12.5	Patent
2008	14	4	16	Patent
1709	14	3	11.2	Patent
1943	13	4	14.5	Patent
1985	13	3.5	10.5	Patent
1960	13	3	9.5	Occluded
2008	13	4	14.5	Patent
1709	13	3	14	Occluded
			Occluded—2 Patent—9	18 per cent

*All graft measurements were made after the graft had been inserted and blood flow restored.

Group II. Freeze-dried Autogenous Grafts.—Because of previous experience with freeze-dried homogenous grafts in the carotid arteries of dogs it was expected that a rather high incidence of relatively early occlusion would be encountered in the Group III grafts. For this reason the dogs containing Group II and III grafts were explored 4 to 6 months postoperatively in order that those in whom the grafts had thrombosed might be sacrificed and not be carried needlessly for the full year.

TABLE II. FREEZE-DRIED AUTOGRAFTS

DOG NUMBER	PERIOD OF FOLLOW-UP (MONTHS)	OUTSIDE DIAMETER OF GRAFT (MM.)	OUTSIDE DIAMETER OF HOST VESSEL (MM.)	LENGTH OF GRAFT (CM.)	RESULT
2270	6	3	4	10	Occluded
2283	5	3.5	4.5	10	Occluded
2290	5	3.5	4.5	12	Patent
2279	5	3.5	3.5	12	Occluded
2432	12	4	4	12	Patent
2177	5	4	4.5	11	Occluded
2442	5	4	5	12	Occluded
1911	12	3.5	4	11	Occluded
2463	12	3.5	4	11	Patent
1883	5	4	4.5	11	Occluded
1915	12	3.5	3.5	10.5	Patent
				Occluded—7 Patent—4	64 per cent

Of the 12 freeze-dried autogenous grafts originally inserted, one was lost to long-term follow-up when a hematoma was discovered on the twentieth postoperative day. A disruption at the upper suture line apparently had occurred. At exploration 4 to 6 months postoperatively, only 5 (45 per cent) of the remaining 11 grafts were patent. Four of these grafts were not disturbed, the exploratory wounds were closed, and the dogs were preserved to complete the follow-up of one year. One patent graft was excised for histologic study.

At the end of the experiment one more of the freeze-dried autogenous grafts had become occluded. The remaining 3 were patent, the suture lines were clean, and there was no true aneurysmal formation, but there was some thinning and uniform dilatation as compared with the actively contracted segments of adjacent host vessel. In all, 7 of 11 (64 per cent) of the grafts had become occluded by the end of one year (Table II).

Group III. Freeze-dried Homografts.—Three of the original 14 grafts in this group were lost to long-term follow-up. One was in the dog whose freeze-dried autogenous graft on the other side was complicated by a suture line disruption. The dog was sacrificed. The other 2 grafts were in dogs that died of distemper at 14 and 18 days, respectively, after operation. Both of these grafts showed some fresh thrombosis but it is doubtful that either was occluded prior to death.

At exploration 4 to 6 months after operation, 4 (36 per cent) of the remaining 11 freeze-dried grafts were patent. All 4 of the patent grafts were left in situ to complete the experiment. At sacrifice of the animals one year after insertion of the grafts the 4 grafts were still patent. Suture lines were clean but in one graft there was a rather large area of recent organizing mural thrombosis in the middle of the graft. There were no aneurysms, but, as with the preserved autogenous grafts, there was relative thinning and uniform dilatation of the excised grafts, in comparison with the contracted host segments. The number (7) and percentage (64 per cent) of grafts occluded were exactly the same as for the freeze-dried autogenous group (Table III).

TABLE III. FREEZE-DRIED HOMOGRAFTS

DOG NUMBER	PERIOD OF FOLLOW-UP (MONTHS)	OUTSIDE DIAMETER OF GRAFT (MM.)	OUTSIDE DIAMETER OF HOST VESSEL (MM.)	LENGTH OF GRAFT (CM.)	RESULT
2270	6	4	3	10	Occluded
2283	6	5	4	13	Occluded
2290	6	3	4	12.5	Occluded
2279	6	3	4	12	Occluded
2432	13	4.5	3.5	13	Patent
2177	6	3.5	4	10	Occluded
2442	6	4	4	12	Occluded
1911	12	3.5	3	11	Patent
2463	12	3.5	4.5	12	Patent
1883	6	3.5	5	10	Occluded
1915	12	4	4	11.5	Patent
				Occluded—7 Patent—4	64 per cent

DISCUSSION

This experiment was undertaken to separate and study factors involved in the success or failure of small vessel replacements. Three major factors which may influence the results obtained with these arterial grafts are the technique used in inserting the graft, the method of preservation of the graft, and a foreign tissue or homograft reaction.

Group I was set up as a control group to evaluate end-to-end anastomosis as a technique for insertion of grafts in vessels of this size (3 to 5 mm. outside diameter). Nine of the 11 grafts in this group (82 per cent) were patent at the end of one year. However, it should be pointed out that in 3 instances an anastomotic site, though not appreciably narrowed, was bridged at one side by one of the continuous mattress sutures which had pulled free of the underlying vessel wall (Fig. 1). Apparently this was the result of growth or expansion at the suture line with a tearing free of the nonabsorbable continuous suture which could not expand with the wall. Although no obstruction to flow was apparent in these grafts which remained patent, it can be conjectured that bridging suture material may have contributed to thrombosis in the 2 grafts which were occluded. On the basis of these observations, it is suggested that the suture lines be interrupted at more than 2 points to minimize the chance of "bridging" observed with the longer continuous sutures.

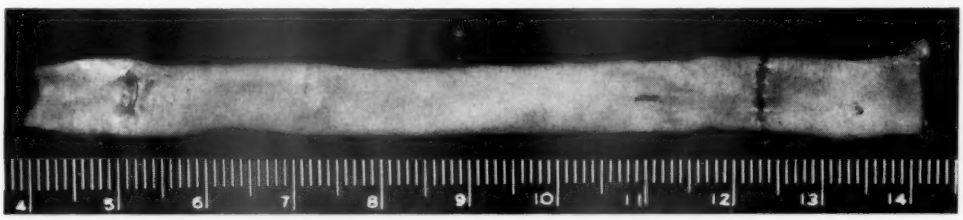


Fig. 1.—The bridging silk suture is shown at the anastomosis on the left. It is to be noted that the well-healed line of anastomosis above and below the bridging suture is free of silk and represents the hemicircumference from which the suture material pulled free.

These results demonstrate that long fresh autogenous grafts can be inserted in these small vessels with reasonably satisfactory results when an end-to-end suture technique is employed. This observation in no sense contradicts clinical experience[2, 7] which has shown that in many situations and for several reasons end-to-side anastomoses are preferable to end-to-end anastomoses in the treatment of occlusive disease of peripheral vessels. However, in comparing the clinical results obtained by end-to-side and end-to-end anastomosis in the insertion of grafts for arterial occlusive disease, a critical evaluation of the technique employed is extremely difficult because of the uncontrollable variable, the disease itself.

A comparison of the results obtained in Group II with those of Group I reflects the detrimental effect of preservation and storage (freeze-drying) on these grafts. With method of suturing unchanged and technique perhaps improved by experience with Group I, the freeze-dried autografts remained patent in only 36 per cent of the dogs. The one documented change in a graft that is

produced by freeze-drying is loss of viability. Although it has not been proved, it is quite possible that this loss of viability is the factor responsible for the difference in results obtained in the 2 groups.

It has been the experience of some,[1, 6] both in the experimental animal and in human beings, that small vessel replacements with fresh autogenous vein segments show a lower incidence of thrombosis than do preserved homografts. Unfortunately, others[5, 7] have not been able to demonstrate this superiority of autogenous vein grafts. In addition, vein grafts are more apt to develop aneurysmal dilatations[3] than their arterial counterparts, unless adequate support can be provided or is provided by surrounding tissues.

Fresh or viable arterial homografts do no better than those which have been devitalized and preserved by freeze-drying.[9] The living cellular elements in the former are lost in a homograft reaction. Perhaps significant improvement of results with long small vessel grafts awaits the solution or control of this reaction. Arterial homografts may then be preserved and implanted as viable structures and, like their autogenous counterparts, be expected to persist as such.

When Group II and Group III are compared, nonviable autografts and homografts preserved by the same method, it is logical to assume that any significant difference in results is a reflection of the difference in reaction of the host to the type of tissue implanted, one native to the individual animal and the other foreign to it. Since there was no significant difference in long-term results with the 2 types of grafts, it may be inferred that a specific homograft reaction plays little part in determining the success or failure of a freeze-dried arterial homograft. Therefore, continued studies and attempts to further "despecify" such nonviable grafts would seem rather pointless. On the other hand we are not justified in assuming that the host reaction to the devitalized tissue in these vessel segments, autogenous or homogenous, may not be a significant factor in contributing to thrombosis and occlusion. A substance which causes less reaction on the part of the host than freeze-dried tissues of the same species could result in a greater degree of success. Further studies with the plastics may discover such a prosthesis but reports to date, including a recent one on the use of Teflon,[4] have been very discouraging in respect to the outlook for satisfactory replacement of these small vessels with synthetic materials.

That individual variation in host reaction to, or acceptance of, vascular replacement substances may be a factor in the end result is suggested by this study. In all but 2 of the dogs with a freeze-dried homograft in one carotid and a freeze-dried autograft in the other, the graft successes or failures were paired. If the freeze-dried autograft in a given dog remained patent, so did the homograft (3 instances). If occlusion occurred on one side, it also occurred on the other (6 instances). A careful review of the protocols revealed no satisfactory explanation for this observation which is provocative of further thought and study.

A late occlusion (after 5 months) of one of the freeze-dried autografts (Fig. 2) and a fresh organizing mural thrombosis (Fig. 3) discovered in one of the freeze-dried homografts at one year point up the inadequacy of short follow-ups and stand as evidence that occlusion may occur in these long small vessel grafts

after several months of patency. Also, there is evidence from this study, particularly in the grafts that for one reason or another were observed short periods of time after implantation and before complete occlusion had occurred, that thrombosis may originate either at (Fig. 4) or away from (Fig. 5) the suture lines. When occlusion had become complete at the time of sacrifice, it was next to impossible, even on careful microscopic study, to decide where in the graft the occluding thrombus had started.

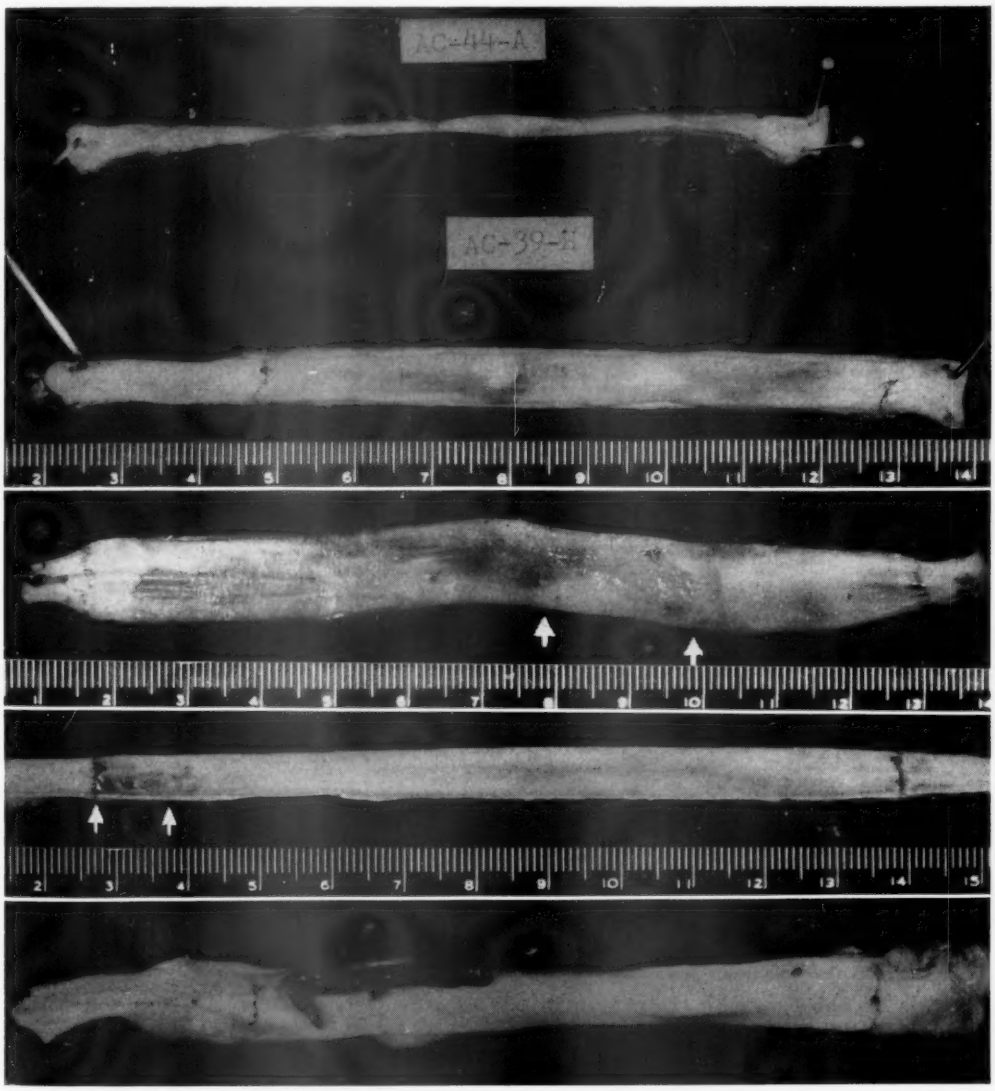


Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 2.—At exploration 5 months after implantation both the freeze-dried autograft (44-A) and the freeze-dried homograft (39-H) were patent. At the end of one year delayed occlusion of the autograft had occurred as illustrated.

Fig. 3.—The fresh mural thrombus found in this patent freeze-dried homograft at the end of one year is indicated by the arrows. The microscopic picture confirmed the impression gained by gross examination that this is a recent organizing thrombus and not an old lesion.

Fig. 4.—The mural thrombus in contact with the suture line on the left is delineated by the arrows.

Fig. 5.—Although the free tail of the thrombus illustrated above extended beyond the suture line, the point of origin and adherence of this thrombotic process is well away from the anastomosis.

GROSS AND MICROSCOPIC COMPARISON OF THE VARIOUS TYPES OF GRAFTS

Grossly, in the excised specimens, the patent fresh autogenous grafts resemble the normal vessel in every respect (Fig. 6). This is in contrast to the freeze-dried grafts which appear uniformly dilated and thin-walled as compared with the actively contracted host vessel segments (Fig. 7). On the other hand, the patent freeze-dried autogenous and homogenous grafts are indistinguishable, one from the other, to gross examination (Fig. 7).

Fig. 6.

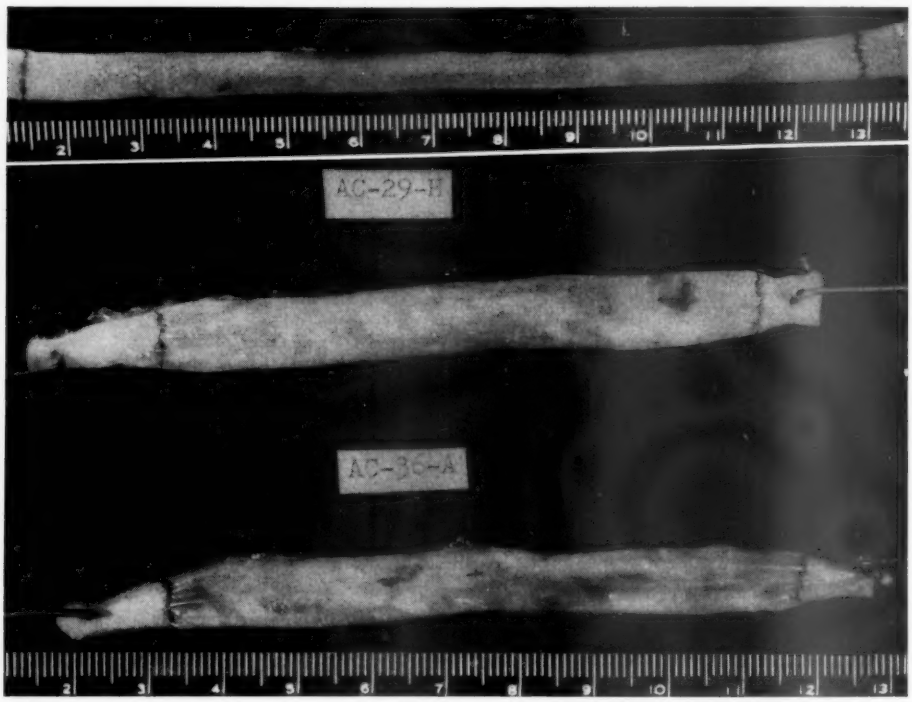


Fig. 7.

Fig. 6.—The fresh autograft above is quite similar grossly to the normal vessel segments at either end of the excised specimen, except for slight narrowing. This latter, however, was not a constant finding in respect to the fresh autografts which, in the main, were indistinguishable from the adjacent vessel segments.

Fig. 7.—The freeze-dried homograft (29-H) and the freeze-dried autograft (36-A) both are dilated and thin-walled as compared with the contracted host vessel segments at the ends. The 2 grafts, however, are indistinguishable grossly one from the other.

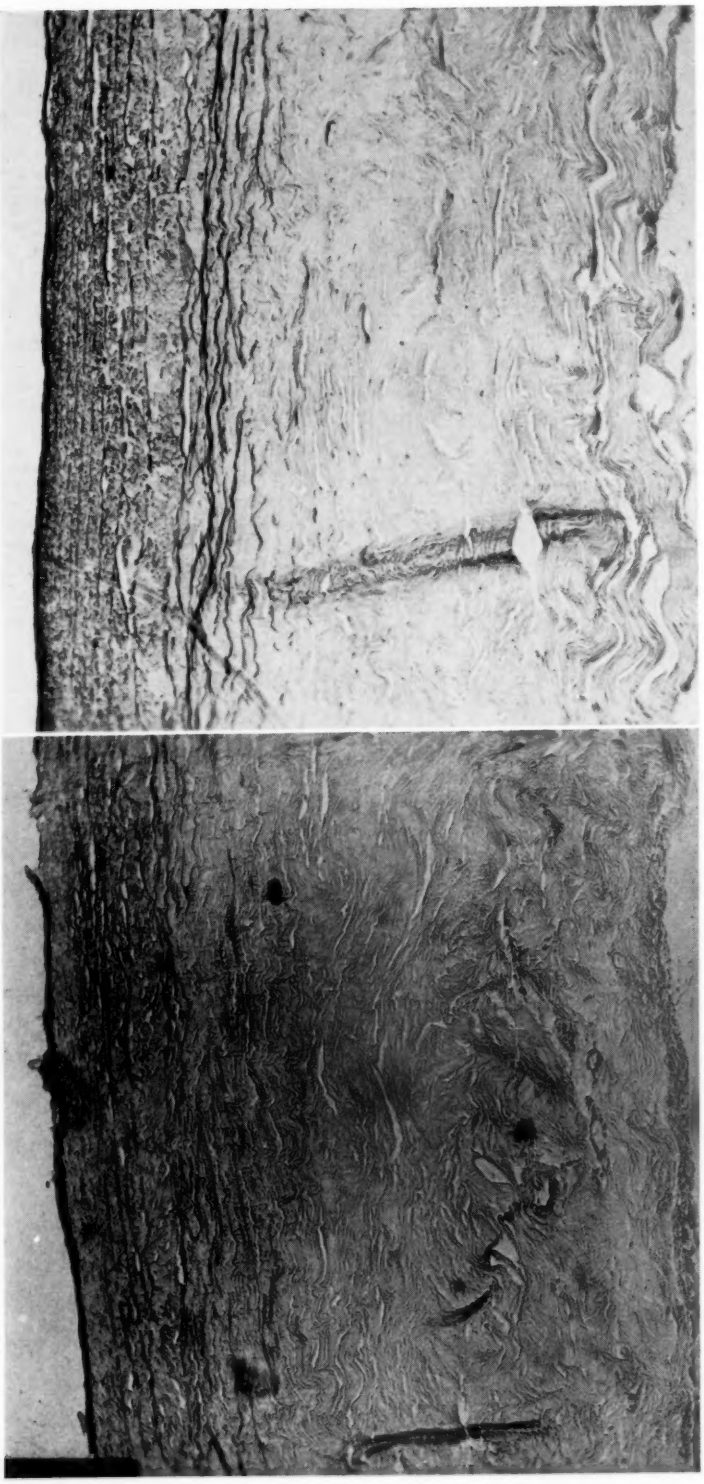
The microscopic findings parallel the gross observations. Away from the suture lines the fresh autogenous graft wall is indistinguishable from that of the adjacent vessel segment (Fig. 8). The picture is entirely different in the freeze-dried grafts (Fig. 9). In both types, autogenous and homogenous, all muscle elements have disappeared from the media with a loss of architecture, condensation and fragmentation of the elastic fiber layers, and over-all thinning of the graft wall as compared with normal vessel wall. Fibrous replacement from the host does not completely compensate in bulk for loss of graft substance.

In the preserved grafts a thickened intimal layer is present at the suture lines and extends in diminishing thickness for varying distances (several millimeters) toward the middle of these long grafts (Fig. 10, *A*). This intimal layer

B.

A.

Fig. 8.—Photomicrograph (×100, ⅔ off reduction, Gomori's aldehyde fuchsin with Foot's modification of Masson's trichrome stain). *A*, section of the wall of a fresh autogenous graft is shown in *A* and of the adjacent vessel wall in *B*. The microscopic pictures are quite similar in respect to over-all architecture, thickness of the media, preservation of muscle cells, and appearance of the elastic fibers. Not well shown at this magnification but present in both sections are endothelial cells lining the lumen.



B.

A.

Fig. 9.—Photomicrographs (×100, 2/7 off reduction, Gomori's aldehyde fuchsin with Foot's modification of Masson's trichrome stain). The wall of a freeze-dried autograft is shown in *A* and of a freeze-dried homograft in *B*. These, although quite similar, present a marked contrast to the normal vessel and fresh autograft sections. The medial layer is thin, the muscle cells have disappeared, and the elastic fibers show fragmentation. The adventitial layer has become thickened presumably by fibrous tissue replacement.

B.

A.

Fig. 10.—Photomicrographs (×100, ⅔ off reduction, Gomori's aldehyde fuchsin with Foot's modification of Masson's trichrome stain). Section *A* is from the wall of a freeze-dried homograft near the anastomosis and section *B* is from the middle of the same graft. In *A* the thickened intimal layer covering the internal elastic membrane is well shown. This layer extends for varying distances from the suture line, up to a centimeter or more, toward the middle of the graft. In *B* the thickened intimal layer is no longer seen and no endothelial cells can be demonstrated.

invariably thins out so that the innermost elastic fibers appear to line a great length of the middle portion of these grafts even at the end of a year (Fig. 10, *B*).

No calcification is demonstrable in the freeze-dried grafts. Neither cholesterol clefts nor foam cells are present (hematoxylin and eosin stain) and the absence of atheromatous change is confirmed by the lipid stain (flaming red–propylene glycol). No consistent difference between freeze-dried autogenous and homogenous grafts could be discovered by careful microscopic examination.

SUMMARY

The problem of small vessel replacement has been revaluated using fresh autogenous, freeze-dried autogenous, and freeze-dried homogenous arterial grafts in the carotid artery of the dog. All grafts were 10 cm. or more in length and were followed for a minimum of one year unless occlusion was demonstrated earlier. The following pertinent observations were made.

1. End-to-end anastomoses may be used for the implantation of fresh autogenous grafts in these small vessels with a reasonable degree of success.

2. Freeze-dried autogenous grafts showed a significantly higher incidence of thrombosis than did fresh autogenous grafts. It is suggested that viability may contribute measurably to the success of long small vessel grafts. At the same time it is recognized that fresh homogenous transplants cannot be expected to persist as viable structures until the homograft reaction is better understood and controlled.

3. Freeze-dried homografts functioned as well as their autogenous counterparts and were indistinguishable from them, grossly and microscopically. This would indicate that a specific foreign tissue or homograft reaction is of little consequence in determining the success or failure of such devitalized arterial homografts.

4. Thrombosis may occur either at or away from the suture lines in long small vessel grafts and occlusion may be delayed until several months after implantation.

5. Individual variation in host reaction to, or acceptance of, a vascular graft may be a factor in the end result, even in the absence of complicating cardiovascular disease.

6. No endothelial layer could be demonstrated throughout a great extent of the central portion of autogenous and homogenous freeze-dried grafts which were still patent at the end of a year.

REFERENCES

1. Anzola, J., Palmer, T. H., and Welch, C. S.: Long Femoral and Ilio-Femoral Grafts, Surg. Forum, Clin. Congress, Am. Coll. Surgeons, 1951, Philadelphia, 1952, W. B. Saunders Company, p. 243.
2. Crawford, E. S., Creech, O., Jr., Cooley, D. A., and DeBakey, M. E.: Treatment of Arteriosclerotic Disease of the Lower Extremities by Excision and Graft Replacement or By-Pass, SURGERY 38: 981, 1955.
3. Dye, W. S., Grove, W. J., Olwin, J. H., and Julian, O. C.: Two to Four Year Behavior of Vein Grafts in the Lower Extremities, A. M. A. Arch. Surg. 72: 64, 1956.
4. Harrison, J. H.: The Use of Teflon as a Blood Vessel Replacement in Experimental Animals, Surg., Gynec. & Obst. 104: 81, 1957.

5. Hoye, S. J., and Warren, R.: Follow-up Studies of Ilio-Femoral Arterial Reconstruction in Arteriosclerosis Obliterans, New England J. Med. **254**: 102, 1956.
6. Hughes, C. W., Jahnke, E., and Seeley, S. F.: Homologous Arterial Grafts and Autogenous Vein Grafts Used to Bridge Large Arterial Defects in Man. A Report on Fourteen Cases, SURGERY **33**: 183, 1953.
7. Linton, R. R.: Some Practical Considerations in the Surgery of Blood Vessel Grafts, SURGERY **38**: 817, 1955.
8. McCune, W. S., and Blades, B.: The Viability of Long Blood Vessel Grafts, Ann. Surg. **134**: 769, 1951.
9. Pate, J. W., and Sawyer, P. N.: Freeze-Dried Aortic Grafts: A Preliminary Report of Experimental Evaluation, Am. J. Surg. **86**: 3, 1953.
10. Sewell, W. H., and Koth, D. R.: Unpublished data.

DISCUSSION

DR. D. E. SZILAGYI (Detroit, Mich.).—I should like to give a brief statement of our own findings in the follow-up study of a group of human arterial homografts.

Two hundred and sixty-nine aortoiliac and femoropopliteal arterial homografts were surveyed 6 months to 4 years after implantation. The conclusions were based upon the observation in 150 cases that had had frequent sequential angiographic investigations and on the histologic findings in 25 cases in which the homografts had been recovered either while still patent or shortly after occlusion.

It was found that true connective tissue replacement of the graft does not take place. Once the graft is inserted, therefore, the permanence of its function to a large degree, and in some instances entirely, depends upon the durability of its own histologic elements. The only tissue component of the homograft that persists histologically intact for at least 3 to 4 years is the elastic tissue. Since the normal aorta has a very rich complement of elastic fibers (the elastic component making up 70 to 80 per cent of the wall), aortic homografts perform well for up to 4 years, and perhaps longer, but there is a progressive diminution of the amount of intact elastic tissue, and after 2 to 3 years evidences of degenerative changes appear in the angiograms. In regard to femoral homografts, histologically the femoral artery is composed predominantly of smooth muscle with only a scanty amount of elastic elements. The complex and perishable smooth muscle elements disappear soon after implantation and the media becomes a band of amorphous collagen of low tensile strength. Apparently in at least one third of these cases this collagen band receives no important connective tissue reinforcement from the host and gradually dilates. While it may still function, such a tortuous dilated graft readily becomes thrombosed. In a somewhat smaller group of cases the graft is invaded by connective tissue to a sufficient degree to assure a fairly durable (3 to 4 years or possibly longer) functional existence. In a small number of cases, the homograft appears to be actively rejected by the host. Such grafts either rupture or thrombose early.

These findings are not unexpected if one considers them in terms of the behavior of homotransplants in general. No homologous tissue of the complexity of a human muscular artery has been successfully transplanted in the past.

We must conclude, therefore, that the human aorta and, in particular, femoral artery have serious deficiencies as vascular substitutes.

We should like to add that we have cogent reasons to believe that the method used in processing the homografts was not a factor in the production of changes we noted.

FEMORAL POPLITEAL ENDARTERECTOMY IN THE TREATMENT OF OBLITERATIVE ATHEROSCLEROTIC DISEASE

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OUR experience with the direct surgery of obliterative atherosclerosis involving the distal aorta and its branches has indicated that patients suffering from this disease can be conveniently divided into 2 categories: (1) those in whom the obstruction lies at some level between the renal arteries and the region of the inguinal ligament and (2) those in whom the obstruction occurs at some level of the arterial tree below the inguinal ligament. The purpose of this paper is to present experience with patients in the second group in regard to long-term results, incidence of intercurrent atherosclerotic manifestations elsewhere in the body, technique of operation, and the place of lumbar sympathectomy when direct arterial surgery is applied as the primary treatment.

GENERAL TECHNICAL PRINCIPLES

In the majority of the lesions dealt with, the technique of semiclosed intraluminal stripping (Fig. 1), which has previously been reported,[1] was used. It is important, however, to be ready to extend the arteriotomy if the obstruction does not yield to gentle dissection with the stripping loop (Fig. 2). The main difficulty in using the stripper occurs when significant calcification is present in the arterial wall.

In reviewing the lesions dealt with from a technical aspect, it is apparent that the obliterative atherosclerotic process is maximum in a segmental fashion in 3 major areas along the femoropopliteal tree (Fig. 3): the region of the common femoral bifurcation, the segment of the superficial femoral artery in the region of the adductor hiatus in Hunter's canal, and the terminal portion of the popliteal artery. Occlusion in the artery between these segments consists of secondary thrombosis plus thickened intima.

Complete dependence upon angiograms in assessing the extent of atherosclerotic involvement can be both confusing and disastrous. It is common for an angiogram to demonstrate obstruction limited to the adductor hiatus when exploration will reveal marked involvement of the upper femoral and lower popliteal segment as well. Conversely, a preoperative arteriogram may show no filling of the distal arterial tree, while operative popliteal angiography will subsequently demonstrate distal tree patency satisfactory for operation. It is our present belief that the status of the distal arterial tree can frequently

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be best evaluated clinically. For example, a patient under 55 years of age who complains only of claudication in the calf can be considered a favorable candidate for operation even in the absence of distal filling at preoperative angiography if he domonstrates a normal femoral pulse at the groin without a murmur and a foot that, in the absence of popliteal and pedal pulses, is warm, pink, and comfortable at rest with no delay in vein filling on dependency after elevation.

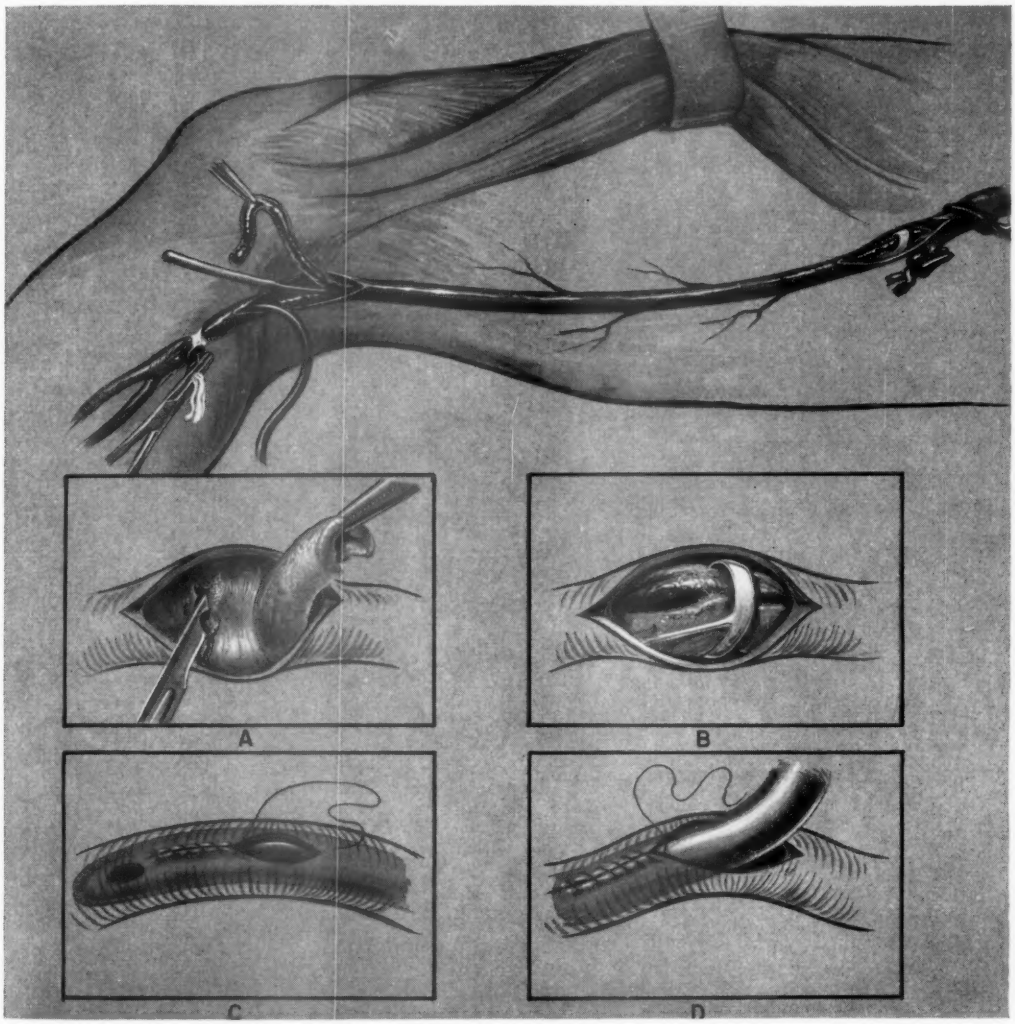


Fig. 1.—Drawing of the essential details of superficial femoral endarterectomy by semiclosed intraluminal stripping. *A*, Beveling of intima to start endarterectomy. *B*, Intraluminal stripper in place. *C*, Closure of distal arteriotomy with catheter in place. *D*, Closure of proximal arteriotomy.

If pulses are restored by operation, it is our belief that the prognosis for long-term improvement is dependent solely upon the rate of progression of the patient's basic disease process. Such a patient runs a serious risk of dying from myocardial infarction but will probably do so with a good pedal pulse in the operated extremity. On the other hand, a patient in any age group who, in addition

to his primary complaint, demonstrates clinically any significant degree of peripheral ischemia, that is, coldness of the foot, discomfort in the toes or arch of the foot on walking, severe claudication in a very short distance, rest pain, and certainly *any* peripheral gangrenous change, has a very poor prognosis, both generally and with regard to the extremity, in spite of the findings at arteriography and the immediate success of the operation in restoring a pedal pulse. Close examination of the distal arteriogram taken at operation in such cases will, at very best, almost invariably show marked plaquing and small areas of partial or complete obstruction throughout the distal arterial tree. It is our feeling that, in this situation where operation has restored a pedal pulse,

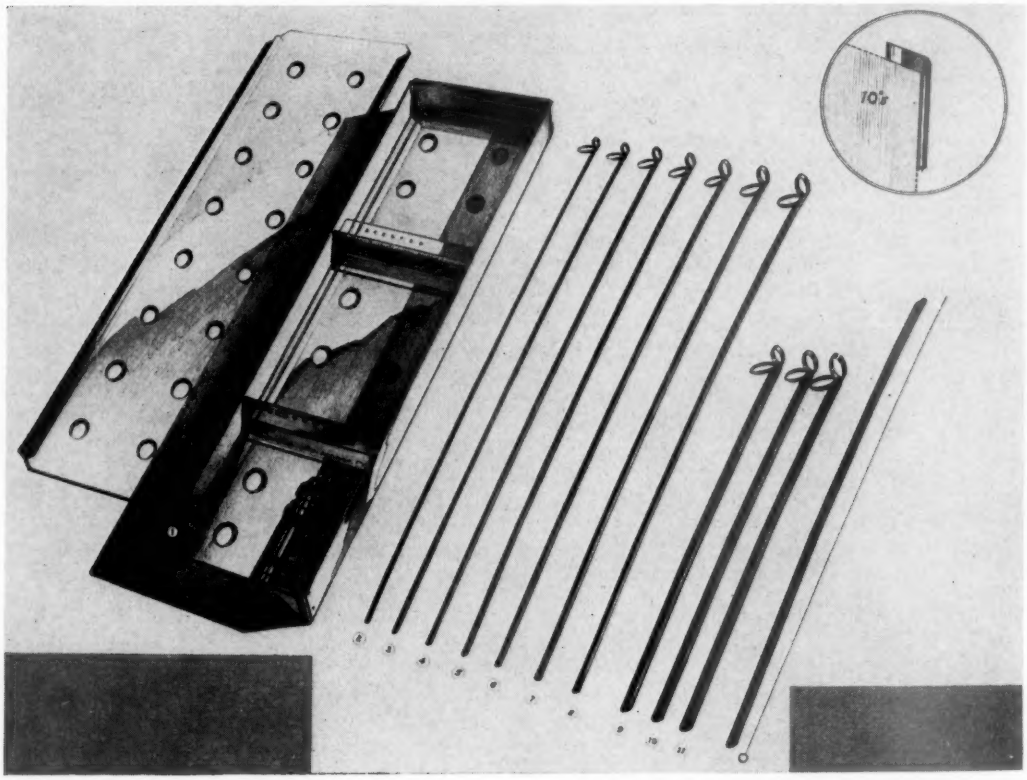


Fig. 2.—A set of stripping loops and container used in performing semiclosed endarterectomy by intraluminal stripping. (Available commercially from A. L. Bresler, 339½ N. Sierra Bonita Ave., Los Angeles 36, Calif.)

prognosis for the extremity is unrelated to technical factors at operation and is entirely dependent upon the rate of progession of the patient's generalized atherosclerotic disease. Further, it is our strong impression that until some reliable therapy becomes available which can at least halt or preferably reverse the progress of the basic disease, little more can be learned about the technique of direct arterial surgery in this area in regard to the relative merits of endarterectomy versus vein graft, versus homograft, versus artificial prosthetic replacement. In addition, the technical skill and judgement of the individual surgeon is a veriable of extreme importance if restoration of pedal pulse is to be obtained. Certainly, the excellence of the immediate result is directly related to the experience of the surgeon who deals with the problem.

General technical principles employed are: (1) increasingly rigid and selective clinical evaluation of patients for direct arterial surgery. (2) insistence upon antecedent or concommitant lumbar sympathectomy, (3) determination of patency of the distal arterial tree in at least one major branch of the popliteal artery by exploration of the popliteal artery and distal operative angiography,

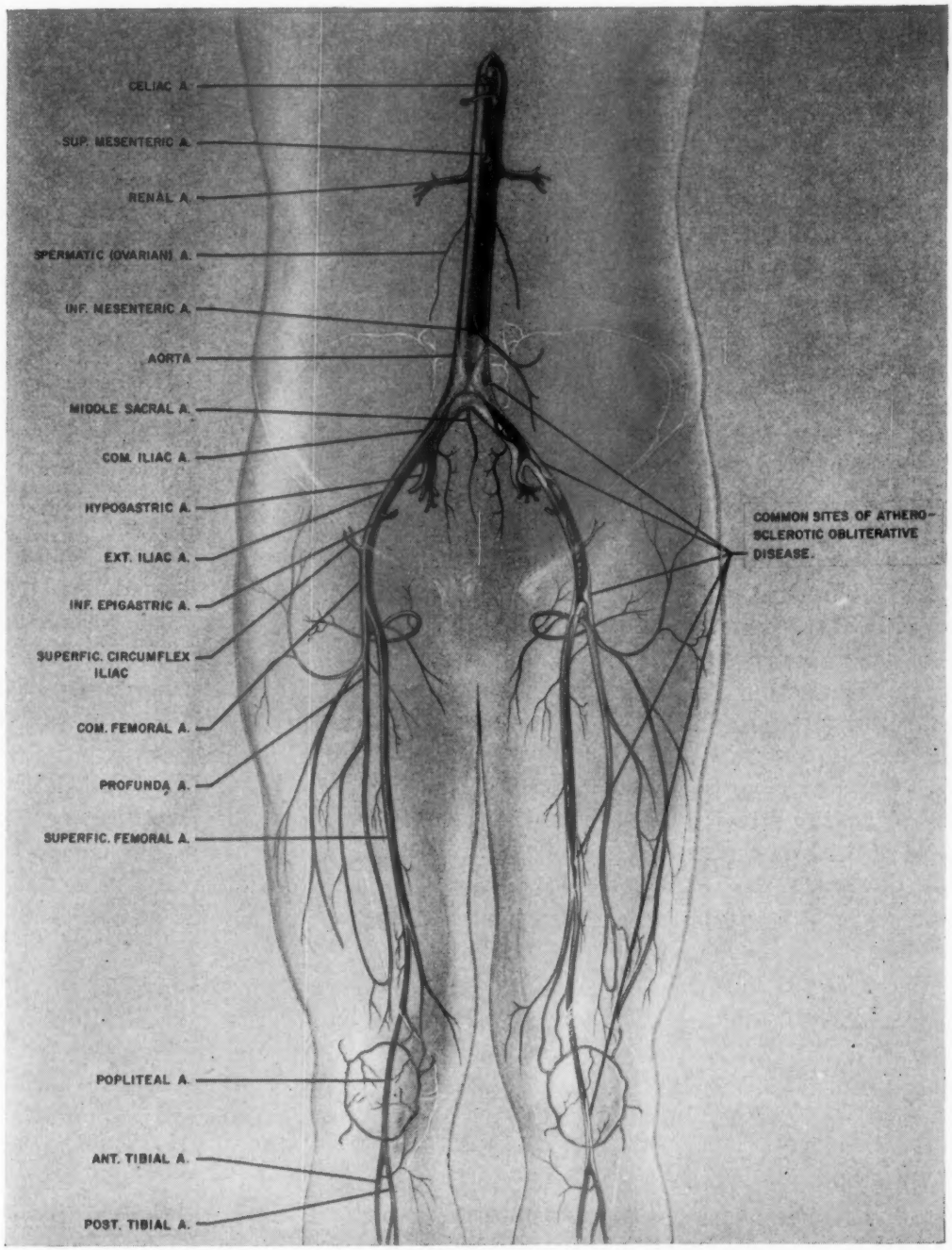


Fig. 3.—Drawing that illustrates the conception of peripheral atherosclerosis as a bifurcational disease of larger arteries, tending to appear in the lower extremity at the region of the bifurcation of the common femoral artery, the adductor hiatus in the region of the geniculate branches, and/or in the region of the popliteal bifurcation.

(4) meticulous efforts to obtain a smooth intimal edge at the distal end of the dissection either by careful beveling or by suturing the intima to the outer arterial wall or both, (5) infiltration of dilute heparin solution into the distal arterial tree during the operation (10 mg. heparin per 100 c.c. saline solution, 5 to 10 c.c. injected into the distal artery every 10 to 15 minutes during the procedure), (6) meticulous dissection of the obliterative core by use of a stripping loop, plus as many supplementary arteriotomies as are necessary, (7) endarterectomy of the full length of the superficial femoral artery, making certain to clear the bifurcation of the common femoral artery and, if necessary, the ostium of the profunda femoris, (8) meticulous preservation of all collateral branches coming off the segment endarterectomized, (9) closure of all arteriotomies over the largest catheter stent that will fit snugly into the endarterectomized segment, (10) intravenous administration of heparin, 25 to 50 mg., just before restoration of blood flow and flushing of the endarterectomized segment with dilute heparin solution as the catheter is removed, (11) maintenance of heparin administration 4 to 6 days after operation (aqueous heparin administered intramuscularly every 4 to 6 hours in an amount to give a blood coagulation time of 10 to 15 minutes when the blood sample is drawn just before the next dose of heparin is due), (12) drainage of the popliteal space for 48 hours, (13) avoidance of encircling dressings, and (14) delay of ambulation until the sixth or seventh postoperative day.

RESULTS

Fifty-nine cases of femoral atherosclerosis have been studied. Follow-up periods extended from 63 months to 9 months on surviving patients. In reviewing these cases, it is immediately apparent that the long-term results in femoral endarterectomy are significantly poorer than in aortoiliac endarterectomy. A study of them permitted a classification of the type of lesion involved so that a prognosis in a given case in regard to favorability for surgery and postoperative outlook would appear to be possible.

On analysis of the results presented below, it becomes immediately apparent that by using direct surgery on the atherosclerotic lesion, the surgeon is trying to deal with a generalized disease by applying a purely local treatment. It would appear that even the best results can be considered as no more than palliative. For purposes of evaluation and discussion, the 59 cases have been divided into 3 groups.

Group I.—Group I (Fig. 4) consists of 16 patients, averaging 54 years of age in whom, by means of arteriogram and direct exploration, the distal arterial tree (Fig. 5) was seen to be without significant evidence of atherosclerotic involvement at the time of operation. In 13 of these patients, pedal pulses were restored for 2 to 56 months. Seven of the 13 have remained asymptomatic 56, 50, 48, 34, 32, 21, and 19 months, respectively. Three of the 13 have enjoyed restoration of pulses and relief of claudication for 47, 35, and 18 months, respectively, but have developed severe atherosclerotic heart disease. Three of the 13 had restoration of pulses and relief of claudication but died suddenly of myocardial infarction 33, 32, and 2 months, respectively, postoperatively.

GROUP I

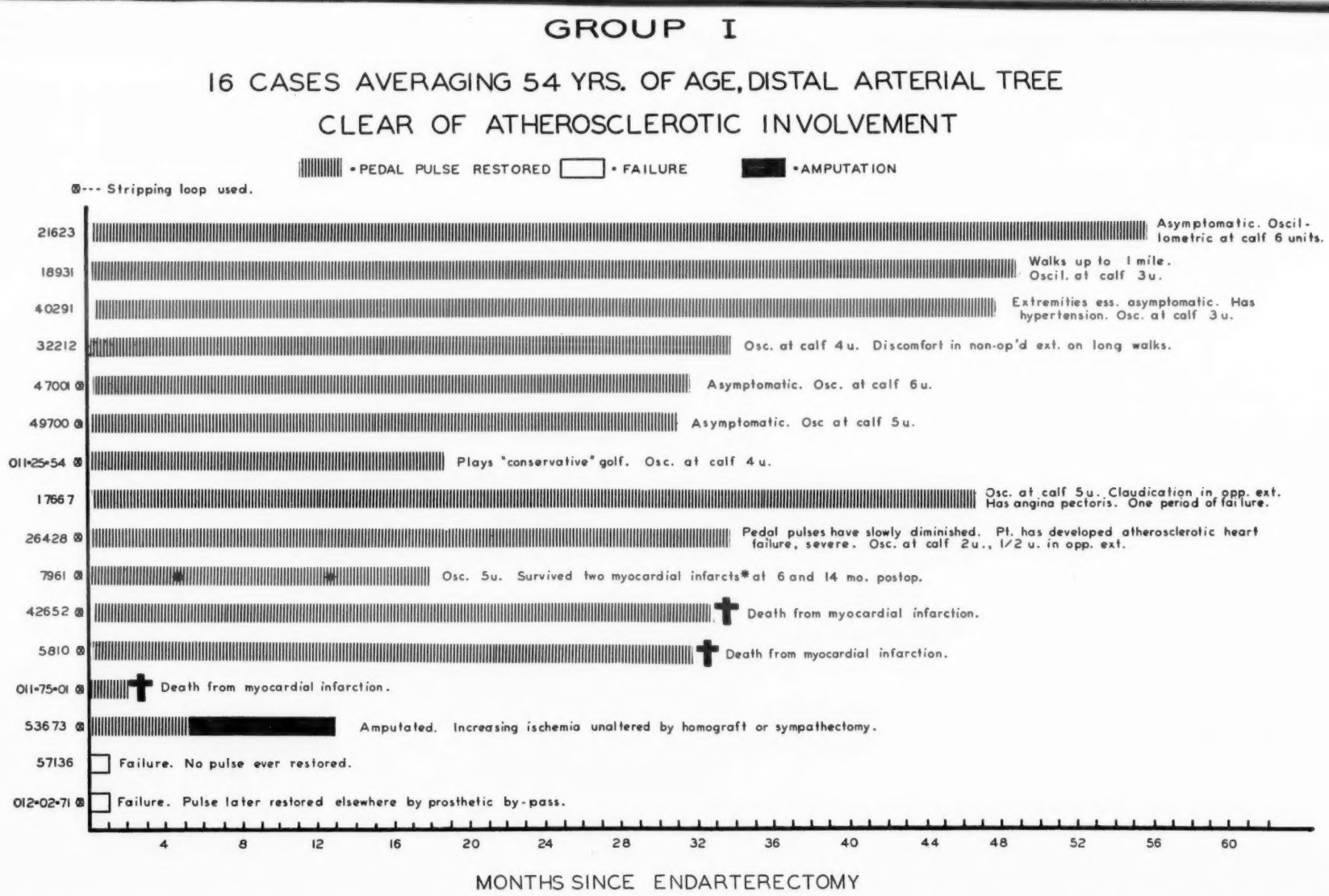


Fig. 4.—Chart of results in cases of femoropopliteal disease treated by endarterectomy in the presence of a distal popliteal tree that is clear of evidence of arteriosclerotic involvement (Group I).

Treatment of 3 of the 16 patients in Group I resulted in failure. Of these 3, one patient had restoration of good pulses in the foot and relief of claudication for 5 months. Gradually claudication developed, however, and amputation was required in spite of an attempted bypass graft and lumbar sympathectomy. Two of the 3 operative failures were considered technical in that no pulse was ever restored.

Fig. 5.—Typical distal popliteal operative angiogram in a case from Group I.

Group II.—Group II (Fig. 6) consists of 27 patients, averaging 58 years of age, on whom 29 operations were performed. In all instances, the distal arterial tree was obviously involved (Fig. 7), but at least one main branch of the popliteal artery was patent at the time of operation. In 14 of the 29 operations a pedal pulse was restored and an improvement in or complete relief of claudication resulted for 4 to 63 months. Four patients on whom 5 operations were performed are asymptomatic, 30, 21, 10, 10, and 10 months, respectively, postoperatively. Two patients showed complete relief of claudication until

death resulted from myocardial infarction 21 and 4 months, respectively, postoperatively. Three patients have shown marked improvement in claudication for 63, 30, and 25 months, respectively, postoperatively but have developed other atherosclerotic complications. Two have severe heart disease and one survived a cerebrovascular accident. Four patients lost some of their initial postoperative improvement but have remained improved over their preoperative status, 23, 21, 15, and 9 months, respectively, postoperatively.

Three of the 27 patients have had weak restoration of pulses and some improvement in claudication for 47, 28, and 23 months, respectively, postoperatively. One of these survived a cerebrovascular accident. Another, a severe diabetic, survived a mild myocardial infarct.

Five of the 27 patients are no better but also no worse in regard to their extremities at 25, 23, 22, and 19 months, respectively, after operation. One of these has developed severe angina pectoris.

Five of the 27 patients had an amputation, 27, 26, 24, 10, and 6 months, respectively, postoperatively. Of these 5, 3 showed marked initial improvement. One patient had a pulse restored, a gangrenous ulcer on the foot healed in another patient, and the third showed a marked improvement of symptoms before gradual resumption of the disease process occurred, leading to gangrene and amputation. Two of the 5 died subsequently of myocardial infarction.

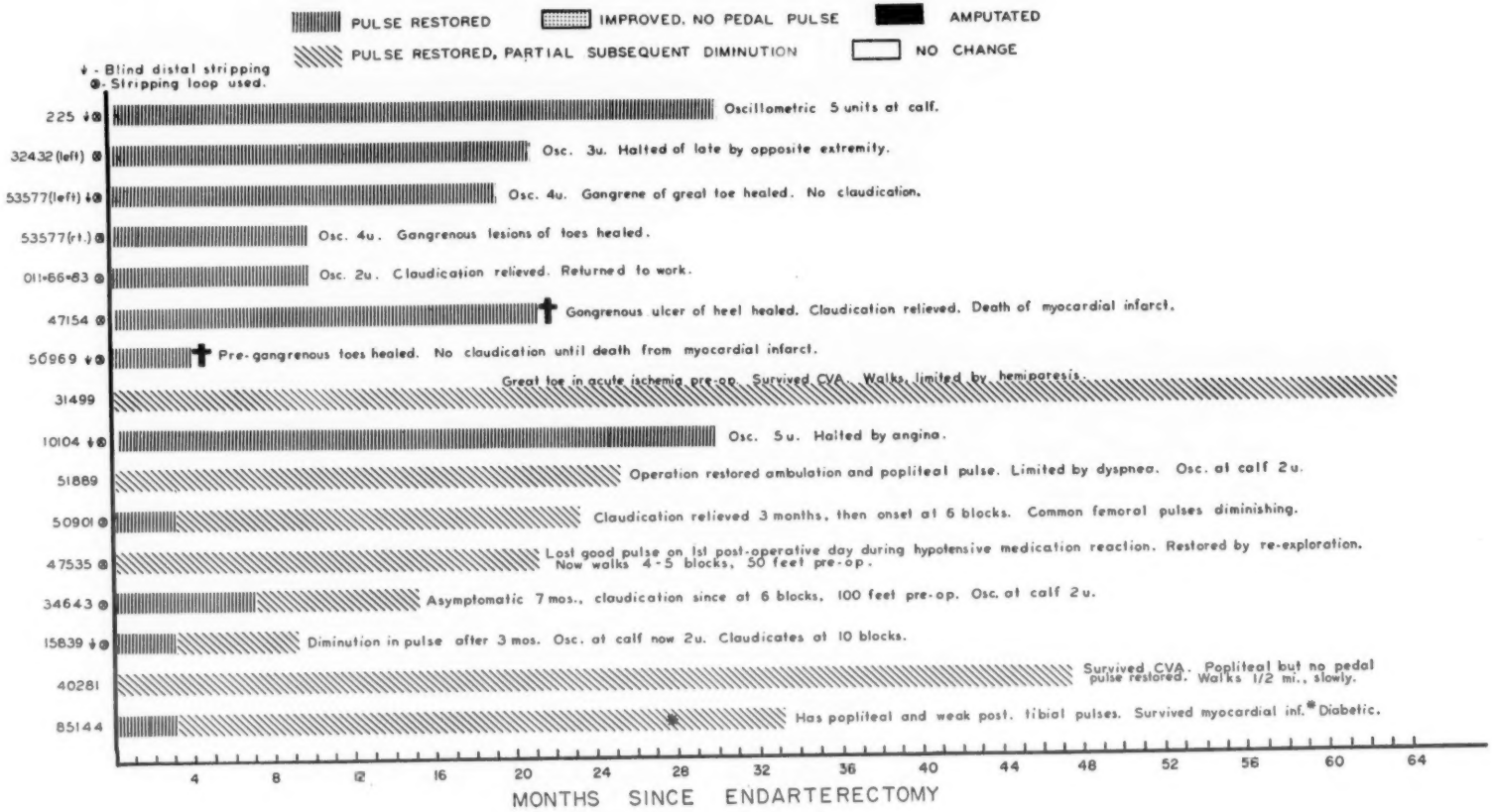
For 2 of the 27 patients the operation was considered a technical failure: one patient died at operation and the second came to amputation in the immediate postoperative period.

Group III.—Group III (Fig. 8) comprises 14 patients averaging 61 years of age, in whom the distal tree was found to be closed both at exploration and by distal operative angiography (Fig. 9). In these patients no pedal pulse could ever have been restored. Two of the 14 patients showed a slight improvement which has been maintained in one for 30 months and was terminated in the other at 26 months by death from diabetes. One of the 14 showed no change 19 months postoperatively. Ten of the 14 patients suffering from chronic severe ischemia at operation had subsequent amputation 1 week to 28 months postendarterectomy. Of these 10, one died 36 months and another 2 months postendarterectomy of myocardial infarction and mesenteric artery occlusion, respectively. One of the 14 patients died in the immediate postoperative period of hemorrhage from the arterial suture line.

Experience With the Technique of Blind Distal Stripping.—In the course of our experience with this problem, occasional cases have been encountered which showed occlusion of the distal popliteal artery at exploration, and angiography at that level resulted in no filling of the distal tree. In some instances, rather than abandon the effort, the distal core was freed, the stripping loop was inserted, and dissection was carried downward in a blind fashion to the level of the bifurcation of the popliteal artery into anterior and posterior tibial arteries below the head of the tibia. In several instances, the stripping loop would

GROUP II

29 CASES AVERAGING 58 YRS. OF AGE DISTAL ARTERIAL TREE INVOLVED BUT AT LEAST ONE MAIN BRANCH OPEN AT OPERATION


PULSE RESTORED
IMPROVED, NO PEDAL PULSE
AMPUTATED
PULSE RESTORED, PARTIAL SUBSEQUENT DIMINUTION
NO CHANGE
↓ - Blind distal stripping
⊗ - Stripping loop used.
225 ↓⊗
Oscillometric 5 units at calf.
32432 (left) ⊗
Osc. 3u. Halted of late by opposite extremity.
53577 (left) ↓⊗
Osc. 4u. Gangrene of great toe healed. No claudication.
53577 (rt.) ⊗
Osc. 4u. Gangrenous lesions of toes healed.
011-66-83 ⊗
Osc. 2u. Claudication relieved. Returned to work.
47154 ⊗
Gongrenous ulcer of heel healed. Claudication relieved. Death of myocardial infarct.
50969 ↓⊗
Pre-gangrenous toes healed. No claudication until death from myocardial infarct.
31499
Great toe in acute ischemia pre-op. Survived CVA. Walks, limited by hemiparesis.
10104 ↓⊗
Osc. 5u. Halted by angina.
51889
Operation restored ambulation and popliteal pulse. Limited by dyspnea. Osc. at calf 2u.
50901 ⊗
Claudication relieved 3 months, then onset at 6 blocks. Common femoral pulses diminishing.
47535 ⊗
Lost good pulse on 1st post-operative day during hypotensive medication reaction. Restored by re-exploration. Now walks 4-5 blocks, 50 feet pre-op.
34643 ⊗
Asymptomatic 7 mos., claudication since at 6 blocks, 100 feet pre-op. Osc. at calf 2u.
15839 ↓⊗
Diminution in pulse after 3 mos. Osc. at calf now 2u. Claudicates at 10 blocks.
40281
Survived CVA. Popliteal but no pedal pulse restored. Walks 1/2 mi., slowly.
85144
Has popliteal and weak post. tibial pulses. Survived myocardial inf.* Diabetic.
4
8
12
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MONTHS SINCE ENDARTERECTOMY

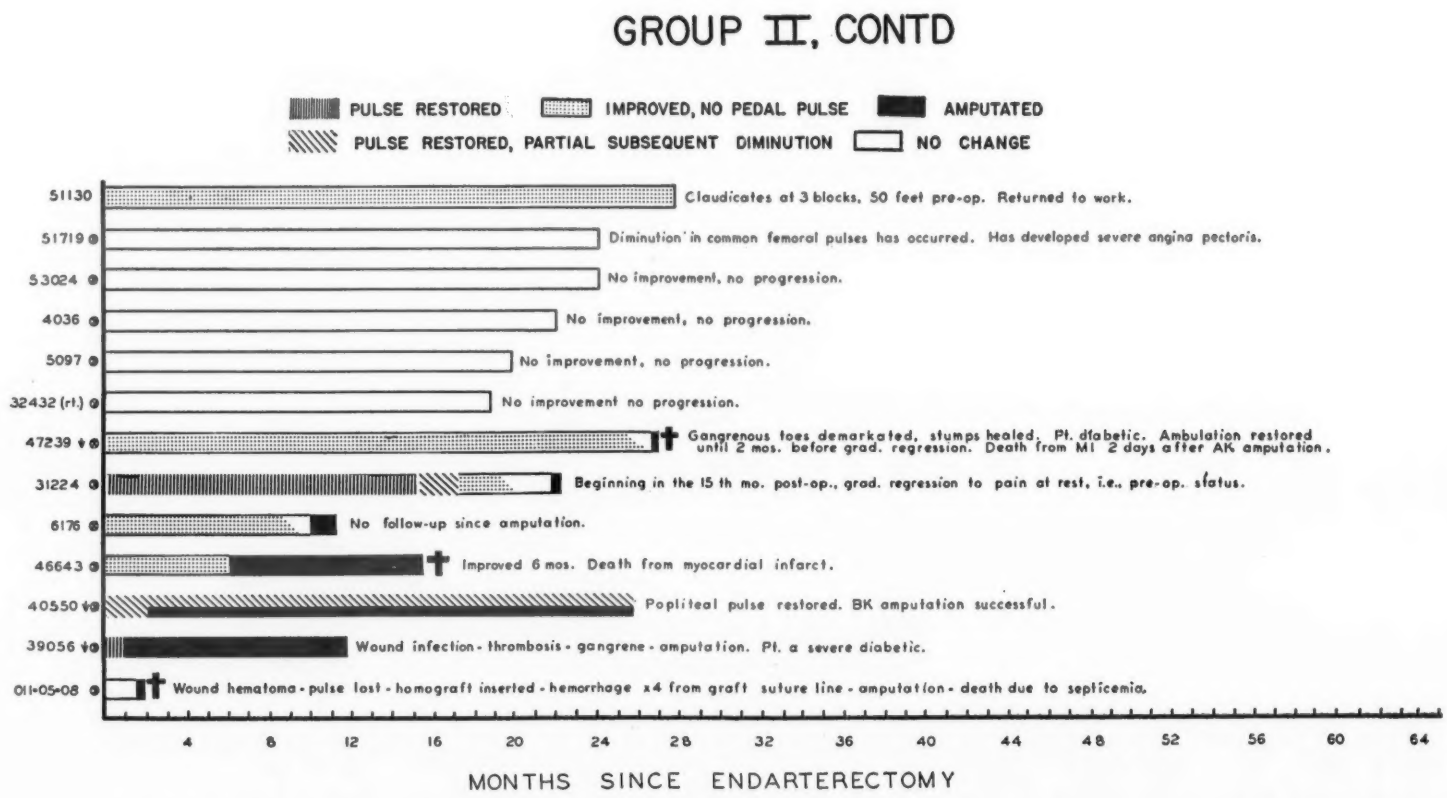

Fig. 6.—Chart of results in cases of femoropopliteal disease treated by endarterectomy in the presence of a distal popliteal tree showing evidence of arteriosclerotic involvement but with at least partial patency (Group II).

suddenly "give" when this level was reached. On withdrawal, a solid core ending in a pointed "tongue" of plaque could then be removed and was followed by vigorous back-bleeding. In such instances, repeat distal arteriography revealed patency through the blindly stripped segment, usually into a patent posterior tibial artery.

Fig. 7.—Typical distal popliteal operative angiogram in a case from Group II.

A total of 8 extremities (among the cases in Group II) were treated in this fashion. In 7 of these a pedal pulse was restored postoperatively. Four of the patients with 5 operations are still enjoying markedly improved distal circulation, and a pedal pulse is present 30, 30, 20, 19, and 9 months, respectively,

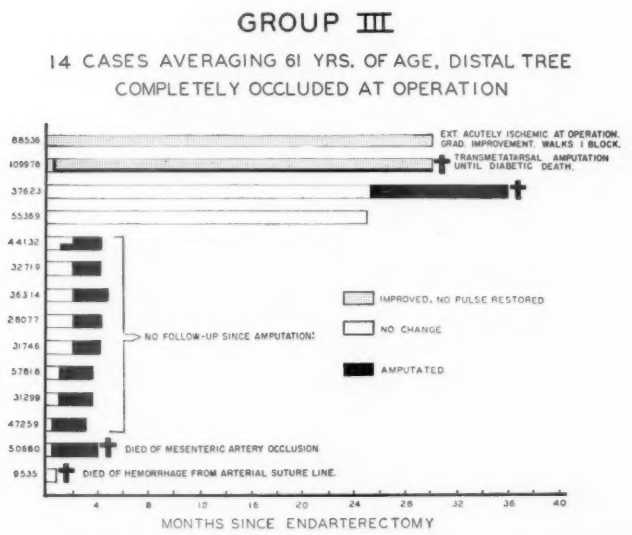

Fig. 8.—Chart of results in cases of femoropopliteal disease treated by endarterectomy in the absence of patency of the distal popliteal tree (Group III).

Fig. 9.—Typical distal popliteal operative angiogram in a case from Group III.

after operation. One patient died of myocardial infarction 4 months after operation with pulse intact until death. One patient did well for 2 weeks and then developed a delayed wound infection; amputation became necessary. One patient had no restoration of pedal pulse but a popliteal pulse was restored, a gangrenous ulcer of the foot healed, and the patient was well for 27 months. Regression gradually occurred, however, and gangrenous changes reappeared requiring amputation. The patient died of a myocardial infarct 2 months later.

DISCUSSION

An interpretation of results, such as those presented above, is extremely difficult because of the problem of setting a comparison standard. If one employs arterial surgery in femoropopliteal disease for the sole purpose of curing intermittent claudication, the results, in general, are discouraging and are comparable to the results obtained by surgical procedures for the cure of cancer. If, on the other hand, the minimum requirement is to prevent amputation and relieve pain, it would appear that the results are somewhat better from a palliative aspect, at least in Groups I and II. It is apparent from the results in Group III that, for the most part, attempts at endarterectomy resulted only in putting the patient through an extra major operation before the inevitable amputation. Arterial surgery would appear contraindicated under these hopeless circumstances.

If one combines the results in Groups I and II with respect to evidence of functional improvement in the involved extremity, then 30 of the 45 operations (66 per cent) gave fair to excellent improvement for significant periods after operation. Six of the 45 operations (13 per cent) were either immediate or eventual failures in that the extremities were finally amputated.

We feel that it is important to point out that in these patients who were treated by endarterectomy there was a striking absence of sudden thrombosis in the endarterectomized segment, in contradistinction to those patients in whom prosthetic replacement or bypass has been employed. Even those patients, who, after enjoying a temporary restoration of pedal pulse, had amputation of their extremities appear to have lost their improvement gradually rather than suddenly. Several of the patients have lost some but not all of their initial postoperative improvement.

In our opinion the most disturbing aspect of this problem is the incidence of intercurrent manifestations of the generalized basic disease process. Of the 43 patients in Groups I and II, 16 (37 per cent) have developed major arteriosclerotic complications, of which 7 (16 per cent) consisted of fatal myocardial infarction.

The absence of sudden failure of pulses in previously endarterectomized extremities and the 36 per cent incidence of intercurrent arteriosclerotic complications in Groups I and II have led us to the firm belief that late failure of direct arterial surgery results primarily from progression of the basic disease rather than from intrinsic operative failure. The difference in the behavior of the grafted extremity compared to the endarterectomized extremity when failure occurs would appear to be the result of mechanical factors. A graft consists

of a shunt. It must be open and functioning at a certain critical flow pressure in order to stay open. An endarterectomized segment is almost certain to be supplied with numerous reopened branches. Distal progression of obliterative disease can consequently occur with the endarterectomized segment remaining open as long as even a small distal outflow is possible. In addition, under the circumstances of distal progression of the disease, it is also possible that the foreign body nature of the graft or prosthesis may have adverse effects resulting in sudden rather than gradual obliteration. Sudden pressure changes might then have a detrimental effect upon the patency of collateral circulation as well, so that acute rather than chronic ischemia in the extremity might be encountered. In other words, it is our impression that failure of an endarterectomized segment results in a gradual return to the preoperative status, which may be compatible with survival of the limb. Failure of the grafted segment, being sudden, may result in the sudden precipitation of an ischemia far worse than that present before operation, which may not be compatible with limb survival. Finally, it is our impression that the bypass graft may turn out to be especially prone to this latter circumstance.

The place of lumbar sympathectomy in the over-all management of the condition defies scientific analysis at our hands. Nevertheless, we have developed a definite opinion in regard to this procedure. Considered alone, it is our belief that if applied to a case where severe ischemic changes are absent, lumbar sympathectomy can be expected to improve collateral circulation in an extremity containing a major arterial occlusion. Improvement of claudication as the result of the procedure is usually minimal or lacking, but protection of the extremity from later onset of grangrenous changes would appear to occur. In short, as a prophylactic procedure against actual gangrenous changes, lumbar sympathectomy is a useful adjunct. The greater the degree of accompanying vasospasm superimposed upon atherosclerotic obliterative changes, the greater the symptomatic benefit of sympathectomy. The procedure, like direct arterial surgery, does nothing about the underlying disease. Progression of relative ischemia on an atherosclerotic basis continues in proportion to the progress of the basic disease process.

Lumbar sympathectomy in combination with direct arterial surgery is additive in benefit. We reach this conclusion on the basis of clinical observation. On the one hand, we have noted that in several of the unsympathectomized, endarterectomized extremities with long-term restoration of pulses the operated extremity is subjectively and objectively cooler. In one of our cases, endarterectomy restored a pedal pulse which diminished in the postoperative period and the foot became increasingly cool. Prompt lumbar sympathectomy resulted in warming of the foot and improvement in the pulse and oscillometric measurement at the calf. A long-term profound improvement has been maintained in this patient both in regard to function and comfort at rest. Restoration of pedal pulse in the immediate postoperative period seems to occur more slowly in the absence of sympathectomy. Conversely, in the sympathectomized extremity, the foot is warmer and the pedal pulse is apt to be of good palpable

quality sooner after operation. Consequently, we have come to the conclusion, at least for the present, that lumbar sympathectomy should precede or accompany femoropopliteal endarterectomy.

It seems to us that the results in the 8 cases in which the blind stripping of the distal popliteal artery was performed deserve special comment. We have long been of the opinion, as we have stated before, that the segment of the arterial tree containing the popliteal bifurcation is especially susceptible to obliterative change. Because of problems involved in the positioning of the patient, the nature of the necessary incisions, and the consequent extension of operating time which would be involved, it has not yet been our practice to expose directly the terminal bifurcation of the popliteal artery which lies well below the knee joint. It would seem apparent that blind stripping was successful because clearing of the popliteal bifurcation was made possible thereby. We cannot help wondering if distal progression in certain of our cases in Group II may be occurring at the level in question. We are certain that one of the failures reported in Group I resulted on this basis. At the time of endarterectomy the distal tree was patent, the intima was markedly thickened. The distal intima was treated by suturing and beveling; a pedal pulse of good quality was restored for a few hours and then disappeared. The foot remained warm and pink, though pulseless, as was its preoperative condition. We elected on this basis not to re-explore the area because of the possibility of jeopardizing the extremity. Pulse in this patient's foot was restored elsewhere after 2 prosthetic bypass procedures. The second distal implantation was lower than the first and both were lower than the distal level of our original endarterectomy. We are not ready to recommend routine use of blind stripping but we wonder if the initial exploration of many such extremities should be at the level of the terminal popliteal artery rather than in its mid-portion just above the knee joint as has been our practice to date. Incisional and positional difficulties can undoubtedly be circumvented in this regard.

Finally, it would seem that some comments on the long-term management of this problem may be pertinent. Unless vigorous efforts can be directed against the generalized progression of atherosclerotic obliterative disease, the good results of direct surgical efforts become sadly diluted by the mere passage of time. It would appear that to date a satisfactory medical management for atherosclerosis is nonexistent. Nevertheless, evidence that dietary habits exert a profound influence upon the incidence of this disease is accumlating at a startling rate. There is a natural tendency for the surgeon especially to view this evidence as a contribution with applications only in the field of Public Health and Preventive Medicine which deal mainly with populations rather than individual patients. Nevertheless, populations are made up of individuals. If the incidence of atherosclerotic disease is high in populations which subsist on a diet high in fat content and total calories and is remarkedly low or almost absent in underfed populations, then the same reasoning must apply to the individual. If the individual is willing to undergo extensive surgery for relief from a disease caused, at least in part, by the content of his diet, then certainly

he should be willing to alter his dietary habits, especially if he obtains symptomatic respite from the surgery. Changing the dietary habits of an adult patient is admittedly a Herculean task, but we believe it is the duty of the surgeon to assist in that task. It is, therefore, our policy in all patients subjected to direct arterial surgery for atherosclerosis to emphasize the importance of a low fat and low calorie diet, plus a weight reduction to the lowest healthy adult weight of the individual. Justification in the form of tangible evidence for this advice is yet to come. Few patients so advised are able to comply. Nevertheless, the alternative at present would appear to be the abandonment of the patient to the natural progress of his disease. In this situation the ultimate value of even the most successful direct arterial surgery will be determined, not by the type of surgery applied, the skill of the surgeon, or his enthusiasm for his particular technique of operation, but by the eating habits of his patient and the metabolic vagaries of that patient's liver in the continuing production of atherosclerotic sludge which silts out into the patient's arteries in an unrelenting fashion day after day. It would seem worth emphasizing that the problem is one of a blood born metabolic disease which affects the arteries only because they are in contact with the diseased blood.

SUMMARY AND CONCLUSIONS

1. Fifty-nine cases of femorolpopliteal atherosclerotic disease followed for 2 to 63 months are presented.

2. The excellence of long-term results appears directly related to the status of the distal popliteal tree, the time of operation, and the severity of the patient's generalized atherosclerotic process.

3. In 45 of the 59 operations where some patency of the distal tree was present at operation, 30 (66 per cent) gave fair to excellent improvement up to 63 months postoperatively. Six of the 45 operations (13 per cent) were failures and the extremities were finally amputated. Sixteen of the 43 patients (37 per cent) developed major atherosclerotic complications, 7 (16 per cent) of which consisted of fatal myocardial infarction.

4. Direct arterial surgery by endarterectomy is contraindicated in the absence of patency in the distal tree as demonstrated by failure of 14 cases when this situation was present; none showed any benefit. Ten of these cases came to early postoperative amputation.

5. Basic principles of technique and management are enumerated and discussed.

6. The importance of antecedent or concomitant lumbar sympathectomy is emphasized.

7. The problem of the underlying disease is discussed.

8. It is concluded that direct arterial surgery by endarterectomy for femoropopliteal atherosclerotic disease is a useful but basically palliative adjunct in the management of the total problem.

9. It is also concluded that failure of the direct surgical procedure is primarily instigated by distal progression of the atherosclerosis in the absence of technical error at operation.

REFERENCE

1. Cannon, J. A., and Barker, W. F.: Successful Management of Obstructive Femoral Arteriosclerosis by Endarterectomy, SURGERY **38**: 48, 1955.

DISCUSSION

DR. WILEY F. BARKER (Los Angeles, Calif.).—I think that whenever we are dealing with femoral artery obstruction, we are dealing with a very diffuse kind of vascular disease which is considerably different from obstruction of the aortic bifurcation or the iliac arteries. People suffering from femoral artery obstruction carry a poorer prognosis from the point of the over-all vascular system. I think it may be seen that recent but late thromboses in the femoral arteries may be due to the fact that we are reaping the harvest of a period of learning or modifying part of the technique. This may have been the time when we were using relatively crude instruments and not clearing a tunnel as accurately as we might now.

I want to emphasize one thing that Dr. Cannon did say. One must be certain that the 3 critical areas in the lower leg are innocent or have been bypassed or endarterectomized; in other words, that the orifice of the superficial femoral, the level of the adductor canal, and the bifurcation of the popliteal are free of disease if one wants a long-persisting open artery. Endothelization of these endarterectomized segments proceeds from the endothelial layer at the end of the segment or from granulation tissue. In the earlier days when we opened the artery from one end to the other, we were providing a source of granulation tissue with relatively prompt endothelization, and it is perhaps important that even now patients from some of our first cases are maintaining excellent pulses in the operated extremities.

DR. J. CUTHBERT OWENS (Denver, Colo.).—In noting the outcome of these cases, 2 complications stand out: first, the high incidence of late postoperative arterial thrombosis at operative sites or elsewhere and, second, the number of amputations resulting from elective arterial surgery.

The first complication is a constant problem to all of us, since we are attempting to correct a major complication of a generalized disease by local treatment. Two years ago at the University of Colorado we noted that many of the patients who had excision and grafting of a peripheral artery later developed arterial thrombosis in a coronary, cerebral, or another peripheral artery. Since then, we have placed all such surgical patients on long-standing anticoagulant therapy. To date, not one of these patients has developed a second thrombosis in a distant vessel. This is a short period of observation. However, we feel that this additional therapy is warranted as prophylaxis for the over-all disease rather than local extremity interest alone. Anticoagulant therapy has been prescribed for nonsurgical patients only if they have had 2 episodes of arterial thrombosis in separate vessels.

The second complication of 15 amputations in 59 elective surgical procedures appears to be a high failure rate. Elective surgery for restoration of arterial continuity should result in fewer amputations than in patients treated conservatively. We recently reviewed approximately 280 patients who had arteriosclerosis obliterans without infection or gangrene and who had been followed over a period of 5 years in one of our vascular clinics without developing indications for arterial surgery. Few were below 60 years of age, and some had died during the 5-year period, but there had not been a single amputation in the group. I do not wish to condemn arterial surgery but only to impress surgeons undertaking these procedures that our objectives are to reduce morbidity, to improve circulation with safety, to remove any adverse local environmental factors, and to prevent further similar complications in other parts of the vascular system.

DR. RICHARD WARREN (Boston, Mass.).—We have had 18 patients of whom 12 were released from the hospital with open segments. Of the 6 who were not, 2 had operations which were technical failures due to perforation of the segment. Two were poorly selected patients in Group III which Dr. Cannon mentioned and 2 had closed segments within hours after the procedure. I think we could have salvaged the last 2 if we had reoperated upon them immediately and inserted grafts, but we did not. That left 12 patients with open

segments. Two of these had segments that closed within about 6 months. One patient died of coronary occlusion 5 months later; his reconstructed segment was open at the time. Nine patients are doing well. The shortest period before closure of the segment is about 7 months and the longest about 18 months. Certain points of technique have been learned. Over half of our patients have had to have multiple incisions. When this has to be done it prolongs the procedure and makes it more difficult than the bypass operation.

I would like to have Dr. Cannon comment on whether it opens or closes the collaterals. In our experience via arteriograms postoperatively, it neither opens nor closes them. We feel safer if we have a graft ready so that we can insert a bypass graft if there is a technical failure with thromboendarterectomy. I believe this is an important point. The question of which patients should be selected is an important one. We feel that it can be used in short blocks and in those without heavy calcification but not in long ones the whole length of the femoral.

DR. JACK A. CANNON.—In answer to Dr. Owens' remarks regarding the incidence of amputations in our series, let me hasten to say that I am as perturbed as anyone regarding this situation. However, you will remember that the bulk of the amputations were encountered in the Group III patients who showed no demonstrable distal arterial tree by operative popliteal arteriography. All of these patients had severe ischemia of the foot, usually with gangrenous changes and severe rest pain. The endarterectomy was performed in a "last ditch" effort to save the extremity. The procedure failed because, in the absence of a patent distal tree, circulation enough to prevent thrombosis in the endarterectomized segment could not be maintained. In those cases where gangrene and rest pain existed, amputation was necessary; we did not feel that the endarterectomy hastened the amputation. Endarterectomy rather was ineffective in preventing amputation in the circumstances outlined.

We have encountered the criticism on occasion in the past and bear it cheerfully as part of the responsibility for being honest. It is our plea, nevertheless, that it be recognized that, with rare exceptions in our series of femoral endarterectomies, amputations have resulted in spite of endarterectomy rather than because of this procedure. If condemnation is in order, it is our belief that the disease rather than the operation is to be condemned.

The regrettable situation that existed among patients in Group III originated from the fact that those who came to amputation after attempted endarterectomy were subjected to 2 operations rather than one to solve the problem. Hence, the main lessons to be learned are (1) the importance of case selection and (2) the fact that the most to be hoped for in the surgical treatment of this disease is some degree of palliation rather than cure. If a patient suffering from this disease complains only of intermittent claudication while playing golf, certainly nothing should be done to jeopardize the extremity regardless of the "possible" benefit. On the other hand, if the patient is about to lose his extremity because of gangrene or ischemic pain, then perhaps more strenuous surgical effort to save the extremity is justified, provided that the chances of doing so are great enough and the patient so desires.

Several of the patients in Group III were eager to submit to any operation that promised even a remote chance of saving the extremity, although they repeatedly refused amputation. Nevertheless, the results in this group have shown us that direct surgical attempts in this situation are, for the most part, futile. On the other hand, certain of the patients in Group II with gangrenous changes and severe pain have been palliated in a highly satisfactory fashion. A patient to whom the function of an extremity is restored, even for a temporary period, usually remains grateful, even though progression of the disease eventually results in amputation.

DIFFERENCES IN TISSUE THROMBOPLASTINS AND THEIR INFLUENCE ON THE CONTROL OF ANTICOAGULANT THERAPY

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INTRODUCTION

PROPER control of the administration of anticoagulant drugs is a major problem associated with this form of therapy. The unfortunate experiences of some clinicians with either excessive hemorrhages or recurrent thromboembolism are contrasted to the highly successful use of these agents by others, both in the active treatment and in the prevention of thromboembolic conditions. Just what constitutes effective and safe control and how to achieve it most reliably are still a matter of some debate.

Most clinicians depend on the results of the so-called one-stage prothrombin assay[15] (determination of "prothrombin time") for the control of anticoagulant therapy. This test measures the rate at which oxalated or citrated plasma clots following the addition of thromboplastin and calcium, the observed clotting time being, ostensibly, a function of the plasma prothrombin content. However, since this assay was first described, advances in the field of blood coagulation have indicated that the results of this test are also influenced by factors other than prothrombin itself, namely by Ac-globulin (Factor V, labile factor, proaccelerin) and by serum prothrombin conversion accelerator (Factor VII, stable factor, proconvertin).[3, 14] In addition, it has been shown that the nature of the thromboplastin itself is critical since various types of this material often produce widely differing results when tested with the same plasma.[2, 4, 11]

Until recently there has been little, if any, knowledge concerning the factors responsible for these differences in thromboplastin activity. However, recent work in our laboratory has indicated the presence of different concentrations of Factors V and VII in various thromboplastin preparations of both commercial and laboratory origin.[9] Similar observations have recently been described by Verstraete, Clark and Wright.[17]

It is the purpose of this paper to present evidence of variations in the nature of different, widely used commercial thromboplastin preparations, based, in part, on their content of certain prothrombin conversion accelerators, and to relate these findings to the difficulties encountered in the control of anticoagulant therapy.

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METHODS

Blood samples were collected by venipuncture using the two-syringe technique. Normal subjects as well as patients receiving a variety of anticoagulant drugs were used as source material as indicated in the text. Nine parts of blood were mixed with one part of 3.2 per cent sodium citrate, and the plasma was separated and used within two hours following collection.

One-stage prothrombin assays were carried out according to the method of Quick[15] using four commercially available thromboplastins and two prepared in our laboratory. Standard curves were prepared for each of the six thromboplastins by averaging the results obtained following serial dilution of four different normal plasmas. However, the bulk of the data reported here has been obtained with three commercial thromboplastins as identified in the text. Standard curves were also prepared for these three thromboplastins in the presence of added Factor V and VII preparations. In all cases where the effects of added accelerators were being studied, one part of the appropriately diluted concentrate was added to nineteen parts of thromboplastin just prior to the start of the assay. The amount of Factor V and VII concentrate chosen was the lowest dilution which did not alter the one-stage prothrombin times of normal plasmas as determined with any of the thromboplastins used.

Two-stage prothrombin determinations were carried out according to the modified technique of Ware and Seegers.[18]

TAMe prothrombin assays were done as described by Glueck, Sherry, and Troll.[8] The same dilutions of the accelerator concentrates as used in the one-stage procedure were added to the TAMe test system immediately before addition of the plasma.

Factor V concentrates were prepared according to the method of Lewis and Ware.[10]

Factor VII concentrates were obtained as described by Alexander, Goldstein, and Landwehr.[1]

RESULTS

In a comparison of six thromboplastins* the results of the one-stage prothrombin determinations carried out on the same plasmas were found to vary widely and, in many cases, over a range of 90 per cent (Fig. 1). This was found to hold true with plasmas having prothrombin concentrations anywhere from 0 to 110 per cent of normal as determined by the more specific two-stage procedure for the assay of prothrombin.[18]

Qualitatively similar results are shown in Fig. 2, which indicates the changes in one-stage prothrombin levels found in a patient following initiation and cessation of Sintrom therapy. It is apparent that the three thromboplastins used produce markedly different results, particularly at the highly critical control level and following withdrawal of the drug.

If, on the other hand, small amounts of Factors V and VII concentrates were added to the one-stage system, it was found that the activities of the three thromboplastins tested were altered, with each individual response apparently being different (Table I). Thus, whereas the activity of thromboplastin 3 was not changed by the addition of the two accelerators, the activity of thromboplastin 2 was more than doubled, and that of thromboplastin 1 only slightly increased. The tentative conclusion to be drawn from these observations would appear to be that the various thromboplastins tested contain different amounts of Factors

*In the text and in all figures and tables the various thromboplastins are identified as follows:

(1) Bacto-Thromboplastins (Difco Laboratories); (2) Simplastin (Warner-Chilcott Laboratories); (3) Soluplastin (Schieffelin & Co.); (4) thromboplastin, "Geigy" (Geigy Co.); (5) human brain, acetone-dried; (6) rabbit brain, acetone-dried.

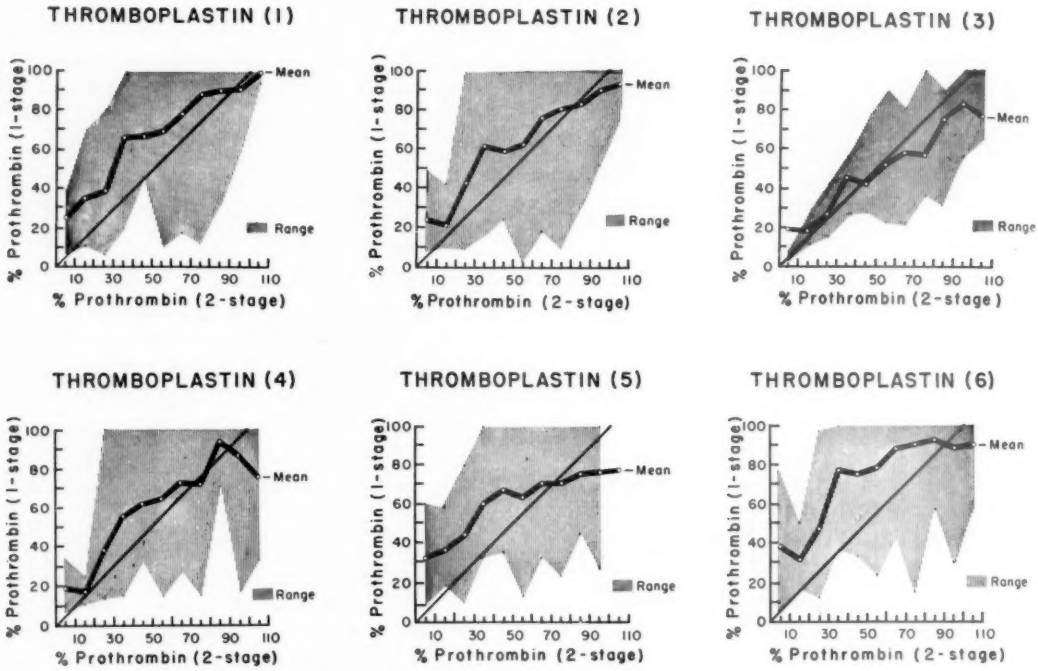

Fig. 1.—Prothrombin values with individual thromboplastins.

The data presented in Figs. 1-3 were collected and processed in the following manner: (a) On the basis of its two-stage prothrombin level each plasma was assigned to a group arbitrarily designated as follows: 1-10 per cent, 11-20 per cent, 21-30 per cent, etc. (b) Using 6 different thromboplastins, one-stage assays were run, in turn, on 12 to 15 plasmas comprising each group. (c) The average one-stage results for the plasmas within each group were plotted against the mid-point of its designated group: 5 per cent, 15 per cent, 25 per cent, etc. This is the mean curve. The spread (range) of the one-stage values was indicated at the same points. (d) The straight line represents the theoretical curve which would result if the one-stage and two-stage values were identical and is included for reference purposes.

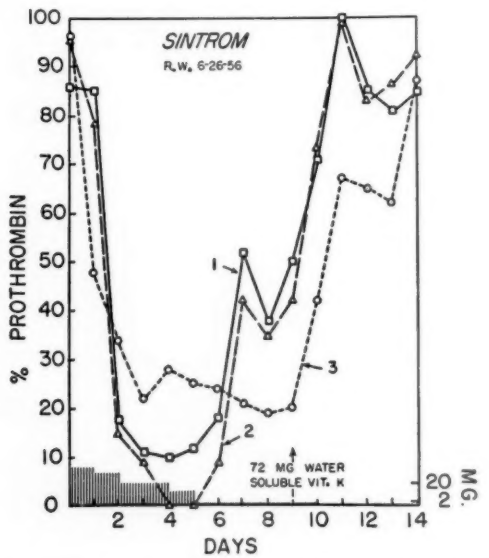

Fig. 2.—One-stage prothrombin curves resulting from Sintrom administration to a single patient. The three curves show the variation in the one-stage assay when three different commercial thromboplastins are used in the test.

V and VII and that these differences are, at least in part, responsible for the variations in the one-stage prothrombin assay results obtained in the absence of added accelerators. This is further supported by the fact that differences between the activities of various thromboplastins are less frequently observed when normal (nontherapy) plasmas are tested, presumably because they contain sufficient amounts of the accelerators to mask the relative deficiencies of the thromboplastins.

TABLE I. THE EFFECT OF THE ADDITION OF FACTORS V AND VII ON THE AVERAGE OF ONE-STAGE PROTHROMBIN VALUES OF THREE PATIENTS ON DIPAXIN THERAPY

	PER CENT PROTHROMBIN	
THROMBOPLASTIN	CONTROL	WITH ADDED FACTORS V AND VII
1	35	46
2	28	68
3	30	33

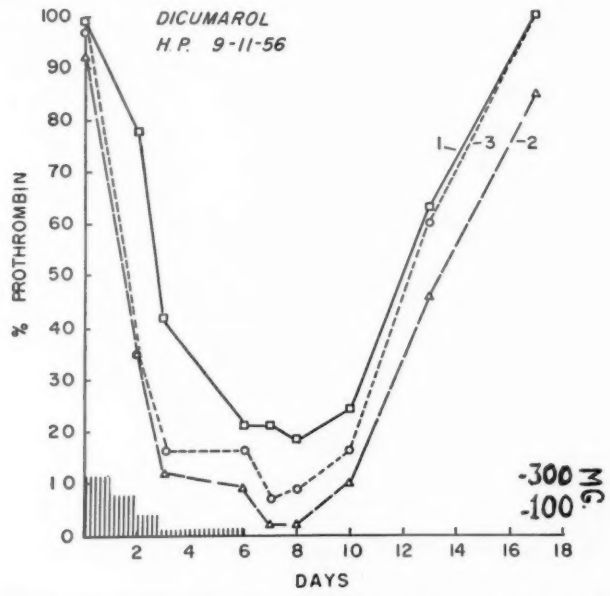

Fig. 3.—TAMe prothrombin curves resulting from Dicumarol administration to a single patient. The three curves show the variation in the TAMe assay when three different commercial thromboplastins are used in the test.

In order to obtain more specific evidence on the contribution of added accelerators to thromboplastin activity, experiments similar to those described above were carried out using the TAMe prothrombin assay[8] instead of the one-stage technique. This procedure is similar in principle to the two-stage method in that it separates the two stages of the clotting mechanism. Complete conversion of prothrombin into thrombin is allowed to occur before the second stage is initiated, thereby providing a more specific system for the study of thromboplastin activity.

The data plotted in Fig. 3 represent the changes in prothrombin levels determined by the TAMe assay as found in a patient following initiation and

cessation of Dicumarol therapy. The results obtained were similar to those produced by the one-stage assay although the variations from one thromboplastin to another are more uniform. Here again the differences are most marked when the patient is in or just above the control bracket.

When small amounts of Factor V and/or Factor VII concentrates were added to the TAMe assay system, it was found that the differences in the results obtained with different thromboplastins could be decreased and, in some cases, abolished (Table II). It is interesting that all three thromboplastins examined behaved differently under these conditions. Thus, whereas the activity of thromboplastin 1 was not altered by the addition of either Factor V or Factor VII, the activity of thromboplastin 2 was increased by the single addition of either accelerator and that of thromboplastin 3 only by the addition of Factor VII. Furthermore, the two less active thromboplastin preparations (2 and 3) had approximately the same activity with both factors added as had thromboplastin 1 by itself. It would appear, therefore, that variations in TAMe assay prothrombin results with different thromboplastins may also be due to variations in their Factor V and VII content. These observations not only lend further support to the tentative conclusions reached from the data obtained with the one-stage assay, but are also in agreement with the results of quantitative determinations of these accelerators in different thromboplastins.[9]

TABLE II. CHANGES IN PROTHROMBIN LEVELS OF THERAPY PLASMAS BROUGHT ABOUT BY THE ADDITION OF FACTORS V AND VII TO DIFFERENT THROMBOPLASTINS (AVERAGE OF 11 EXPERIMENTS)

	PER CENT PROTHROMBIN			
THROMBOPLASTIN	CONTROL	WITH FACTOR V	WITH FACTOR VII	WITH FACTORS V AND VII
1	22	19	20	18
2	11	18	19	20
3	10	9	21	19

DISCUSSION

There is a growing body of evidence to indicate that, in addition to lowering prothrombin, various "prothrombin" depressants also influence the levels of other plasma coagulation factors. Furthermore, it appears that the type of response obtained with various drugs may be different and may for the same drug, vary from patient to patient. A lowering of the Factor VII content of plasma seems to be universally associated with the depression in prothrombin, whereas changes in Factor V activity have been observed less frequently.[6, 19] In addition, levels of certain plasma factors concerned in the in vivo formation of intrinsic thromboplastin have recently been shown to be influenced by the administration of "prothrombin" depressants.[5, 12, 16] The possibility that effects on still other essential coagulation factors, accelerators and/or inhibitors, may not as yet have been recognized should not be discounted at this time. The concentrations of all the factors now known to be affected are decreased more or less rapidly and to varying extents as long as therapy is continued, and return to normal levels at varying rates once the drug is withdrawn.

Of particular interest in this connection are the observations by Ferguson and Patch[7] that, in the one-stage assay, excessively high Factor V levels can compensate for moderately low prothrombin and Factor VII levels, although high Factor VII concentrations do not compensate for low prothrombin or Factor V levels.

It would appear, therefore, to be of particular importance in the control of anticoagulant therapy to measure the combined changes in all clotting factors produced by a given drug rather than its effect on prothrombin concentration only. Since different thromboplastin preparations have been shown to contain different amounts of some of the very accelerators whose plasma levels are affected by anticoagulant drugs, it follows that they may mask to a more or less marked degree the interference with the over-all clotting system brought about by therapy. In order to determine the combined changes in the levels of prothrombin, accelerators, and inhibitors, a thromboplastin preparation should be used which is devoid of or, at least, as deficient as possible in all of the plasma-clotting factors affected by the administration of the drug. Only under these conditions can there be any certainty that the over-all effect of a given drug on a patient's plasma is not obscured by use of a thromboplastin capable of altering plasma deficiencies.

Of the thromboplastin preparations available at this time, those having the greater deficiencies would appear to be the preferable ones to use.

However, our experience with different commercial thromboplastins over a period of three to four years indicates that the accelerator content of freshly obtained and tested preparations may not necessarily remain unchanged from year to year. Thus, whereas recently purchased supplies of two of the thromboplastins tested in this study had characteristics closely similar to those exhibited by supplies of the same manufacture obtained and tested two and three years ago, this was not found to be the case with the third thromboplastin. These findings indicate the necessity for periodic checking of any commercial preparation in order to be certain that batches or lots of a preparation found suitable at any given time will continue to have the same desirable characteristics in the future.

The ideal thromboplastin, then, for use in the control of anticoagulant therapy should have reasonable stability, uniform reactivity both from lot to lot and year to year, and be one which is free of any known factors influenced by anticoagulant drugs. The fact that all thromboplastins used currently are tissue extracts is probably the major reason for the difficulty in preparing identical, uniform preparations, and there would appear to be real doubt as to the possibility of ever preparing the ideal thromboplastin from such sources. However, the possibility of obtaining a synthetic preparation as suggested by the report of Nour-Eldin and Wilkinson[13] seems to deserve further investigation. Various types of such synthetic thromboplastins have recently been prepared in our laboratory and are currently being tested with respect to their accelerator and/or inhibitor content as well as their storage characteristics. Preliminary results of this work have been encouraging.

SUMMARY

1. There is a growing body of evidence to the effect that prothrombin-depressant drugs influence coagulation factors other than prothrombin.

2. In the one-stage prothrombin assay (the determination of "prothrombin time") which is used almost universally to control the administration of these drugs, the nature of the thromboplastin used is a highly critical factor in the result obtained. It is also a critical factor in the results obtained with two-stage prothrombin assay procedures although such influences can be minimized by the stepwise nature of these tests.

3. Different thromboplastins, of whatever source, contain varying amounts of some of the very accelerators, Factors V and VII, whose plasma activities are decreased as a result of anticoagulant therapy.

4. The different and varying concentrations of these accelerators in the various thromboplastins account, at least in part, for the varying results obtained in prothrombin assays. This variability of the nature of different thromboplastins is particularly accentuated in the one-stage assay system where slight variations in clotting times are interpreted as reflecting wide differences in "prothrombin" content. These variations, in turn, may be the most important factor in the wide difference of opinion regarding the efficacy and safety of anticoagulant therapy.

5. The desirable characteristics of an ideal thromboplastin and the possibility of obtaining such a preparation synthetically have been discussed.

REFERENCES

1. Alexander, Benjamin, Goldstein, Robert, and Landwehr, Greta: The Prothrombin Conversion Accelerator of Serum (SPCA): Its Partial Purification and Its Properties Compared With Serum Ac-Globulin, J. Clin. Invest. **29**: 881, 1950.
2. Bassen, Frank H.: The Variability of Prothrombin Time Determinations With "Standardized Thromboplastin Preparations," J. Mount Sinai Hosp. **22**: 112, 1955.
3. Biggs, Rosemary, Douglas, A. S., and Macfarlane, R. G.: Action of Thromboplastic Substances, J. Physiol. **122**: 554, 1953.
4. Conley, C. L., and Morse, W. I.: Thromboplastic Factors in the Estimation of Prothrombin Concentration, Am. J. M. Sc. **215**: 158, 1948.
5. Duckert, F., Flueckiger, P., and Koller, F.: Clotting Factor X. Physiologic and Physico-chemical Properties, Proc. Soc. Exper. Biol. & Med. **90**: 17, 1955.
6. Fahey, J. L., Olwin, John H., and Ware, Arnold G.: Effect of Dicumarol on Ac-G and Prothrombin Activity, Proc. Soc. Exper. Biol. & Med. **69**: 491, 1948.
7. Ferguson, John H., and Patch, Mary Jane: Determinants of the So-called "Prothrombin Time," Proc. Soc. Exper. Biol. & Med. **93**: 193, 1956.
8. Glueck, Helen I., Sherry, Sol, and Troll, Walter: Assay of Plasma Prothrombin With a Synthetic Substrate, Proc. Soc. Exper. Biol. & Med. **87**: 646, 1954.
9. Koppel, J. L., Mueller, Dorothy, and Olwin, John H.: Unpublished observations.
10. Lewis, M. L., and Ware, A. G.: A Simple Procedure for Separation of Prothrombin and Accelerator Globulin From Citrated Human Plasma, Proc. Soc. Exper. Biol. & Med. **84**: 636, 1953.
11. Markley, Judith A., and Dryer, Robert L.: A Comparison of Commercial Preparations of Thromboplastin, Am. J. Clin. Path. **25**: 714, 1955.
12. Naeye, Richard L.: Plasma Thromboplastin Component: Influence of Coumarin Compounds and Vitamin K on Its Activity in Serum, Proc. Soc. Exper. Biol. & Med. **91**: 101, 1956.
13. Nour-Eldin, F., and Wilkinson, John H.: The Separation of Human and Bovine Plasma Thromboplastin With Ether and a Study of Its Properties, J. Physiol. **132**: 164, 1956.
14. Owen, Charles A., Jr., and Bollman, Jesse L.: Analysis of the One-Stage Test for Prothrombin Time, J. Appl. Physiol. **5**: 515, 1953.

15. Quick, A. J., Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190**: 501, 1935.
16. Sise, Herbert S., Kimball, Delbert M., and Adamis, Dionysios: Plasma Thromboplastin Component (PTC) Deficiency Produced by Prolonged Administration of Prothrombopenic Anticoagulants, Proc. Soc. Exper. Biol. & Med. **89**: 81, 1955.
17. Verstraete, Marc, Clark, Patricia A., and Wright, Irving S.: Problems in the Use of Different Tissue Thromboplastins in the Control of Anticoagulant Therapy, Proceedings of the 29th Scientific Sessions, American Heart Association, Oct. 26-29, 1956.
18. Ware, A. G., and Seegers, W. H.: Two-Stage Procedure for the Quantitative Determination of Prothrombin Concentration, Am. J. Clin. Path. **19**: 471, 1949.
19. Wicke, G.: Einleitung der Antikoagulantientherapie mit kurz- und langwirkenden Dicumarinen, Proceedings of the First International Conference on Thrombosis and Embolism, Basel, 1954, Benno Schwabe & Co., p. 739.

Discussion

DR. HENRY SWAN (Denver, Colo.).—I would like to ask a question of Dr. Olwin which was not quite clear to me. When you add this material to the thromboplastin do you raise or lower the reading in terms of per cent? What effect does this have on the reading when you add these agents to the material?

DR. JOHN H. OLWIN (Closing).—The addition of either or both of these factors will shorten the prothrombin time by increasing the activity of the thromboplastin. The degree of shortening will depend on the amount of either or both factors already present in the thromboplastin and in the plasma being tested. The addition of these factors to a thromboplastin low in these factors will increase its activity and will therefore shorten the prothrombin time, and the prothrombin per cent will be registered as higher than it actually is. Hence, if the patient's prothrombin actually is at 5 per cent, you may get a reading of 15 or 20 per cent. Some companies test their thromboplastins on both normal and therapy plasmas and this will reduce the error to some extent. It is important, also, that thromboplastins from the same company may vary in their activity from lot to lot and particularly from year to year.

A COMPARISON OF THORACOLUMBAR SYMPATHECTOMY AND ADRENALECTOMY WITH ADSON SYMPATHECTOMY IN THE TREATMENT OF SEVERE ARTERIAL HYPERTENSION

A Three-to-Seven-Year Follow-up Report

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SUBTOTAL or total adrenalectomy combined with a limited sympathectomy has been used at the Hospital of the University of Pennsylvania for more than seven years as a form of surgical treatment for severe essential hypertension.[7, 9] The purpose of this article is to compare the results of treatment of two similar groups of patients, of which one group was treated by this operative procedure and the other by a bilateral thoracolumbar sympathectomy.[8] Most of the patients had the same surgeon (H. A. Z.). All had severe hypertension and have been followed by the same group of physicians from three to seven years.

From our previous experience with thoracolumbar sympathectomy it became apparent that this procedure was not completely satisfactory due to postoperative morbidity, prolonged postural symptomatic hypotension, and a high incidence of blood pressure relapse. Our results,[8] however, have been similar to those of other investigators who have reported larger series of patients.[4, 5]

Following a modified Adson sympathectomy and bilateral adrenalectomy, either total or 90 to 95 per cent subtotal, the course of our patients has been sufficiently encouraging that we have come to employ this procedure almost exclusively for the surgical treatment of hypertension. It has the advantage of less postoperative morbidity and so far seems to avoid the late return of severe hypertension.

We have performed a total or subtotal adrenalectomy and a limited sympathectomy in 116 patients (Table I) prior to three years ago. Most of these had a modified sympathectomy consisting of resection of the sympathetic chain from the twelfth thoracic through the second lumbar ganglion and resection of the splanchnic nerves (Fig. 1). One hundred and fourteen patients were

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*St. Luke's Hospital, New York City.

**Public Health Service Research Fellow of the National Heart Institute.

treated by thoracolumbar sympathectomy (T_6 through L_3) (Table II) and have been followed for a similar period of time. In this report the first group will be referred to as "adrenalectomy" and the second as "sympathectomy." The average period of follow-up for those surviving the operation in the patients with "sympathectomy" was 4.75 years and in the patients with "adrenalectomy" was 4.20 years (Table II).

TABLE I. OPERATIVE PROCEDURES DESIGNATED AS "ADRENALECTOMY"

TYPES OF OPERATIONS	OPERATED UPON	SURVIVING
Subtotal adrenalectomy and Adson sympathectomy	59	40 (68%)
Total adrenalectomy and Adson sympathectomy	44	31 (70%)
Total or subtotal adrenalectomy and Smithwick type of sympathectomy*	13	8 (61%)
Total	116	79 (68%)

*Seven of these patients had "adrenalectomy" following an unsatisfactory response after "sympathectomy."

TABLE II. DURATION OF FOLLOW-UP OF SURVIVING PATIENTS

YEARS	"SYMPATHECTOMY"	"ADRENALECTOMY"
3-4	15	24
4-5	14	25
5-6	31	20
6-7	23	10
Total	83	79
Average	4.75 years	4.20 years

The average follow-up period is slightly longer in the sympathectomy group.

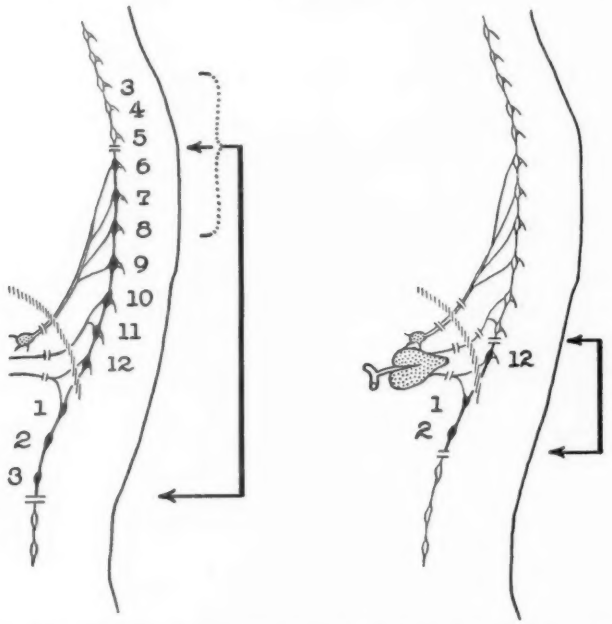

Fig. 1.—In the thoracolumbar sympathectomy ("sympathectomy") we have removed the sympathetic ganglia and trunk from the sixth thoracic to the third lumbar inclusive. The combined adrenalectomy and sympathectomy has included resection of 90 to 100 per cent of adrenal tissue and the sympathetic trunk and ganglia from the twelfth thoracic to the second or third lumbar inclusive, as well as the splanchnic nerves in the group designated as "adrenalectomy." The celiac ganglion was not removed in either operation. The shaded area represents the diaphragm.

We have used Smithwick's classification of patients with hypertension. We are aware that none of the present classifications of the severity of hypertension are adequate in all respects and that they lack a factor for estimating the rate of progress of the patient's disease. The average Smithwick grouping of patients who had a "sympathectomy" was 3.11, and of those who had an "adrenalectomy" was 3.20 (Table III).

TABLE III. SMITHWICK CLASSIFICATION

GROUP	"SYMPATHECTOMY"	"ADRENALECTOMY"
I	2	0
II	38	31
III	19	31
IV	55	54
Total	114	116
Average	3.11	3.20

The distribution according to the severity of their hypertension by Smithwick classification in 114 patients who were treated by thoracolumbar sympathectomy ("sympathectomy") and 116 who were treated by total or subtotal adrenalectomy and a modified sympathectomy ("adrenalectomy"). It is apparent that the patients had hypertension of comparable severity and that many had very severe disease (Grade IV).

The criteria used for the selection of these patients for operation have remained essentially unchanged since previous reports.[2] These include: (1) severe disease as measured by diastolic pressures of 120 mm. Hg or greater, (2) evidence of progressive vascular damage to the brain, heart, eyes, or kidney, (3) failure to respond to vigorous medical therapy, (4) age of not more than 55 years (Table IV), and (5) no vascular accident to the brain or heart within the past six months. Initially those with advanced renal failure were accepted for operation, but it was soon learned that these patients did not respond favorably. Subsequently we have considered as contraindications to either operative procedure phenolsulfonphthalein excretion of less than 15 per cent in 15 minutes and a blood urea nitrogen consistently above 20 mg. per cent.

TABLE IV. AGE OF PATIENTS

AGE (YEARS)	"SYMPATHECTOMY"		"ADRENALECTOMY"	
	LIVING	DEAD	LIVING	DEAD
10-19	1	–	1	1
20-29	8	2	6	2
30-39	21	7	11	5
40-49	48	12	44	18
50-59	5	10	17	11
Total	83	31	79	37
Average	41 years		44 years	

It will be noted that the majority of patients were in their third and fourth decades. Among those who had adrenalectomy a larger number were in the fifth decade than among those chosen for sympathectomy.

It is essential that patients considered for adrenalectomy understand the importance of daily steroid replacement therapy following total or subtotal adrenalectomy. Only those patients who were judged to be capable of continuing this therapy were recommended for this operative procedure. Only one death can be attributed to failure to continue steroid replacement therapy in this series, now numbering 176 patients.

With the adrenalectomy series we have included a few patients who had an initial thoracolumbar or Peet sympathectomy followed by a sufficiently poor result to warrant subsequent adrenalectomy. Both operative procedures were performed through a subcostal incision. The second stage was completed 10 to 14 days following the first operation in most instances.

MORTALITY, SURVIVAL, AND CAUSE OF DEATH

The operative mortality (Table V) for "sympathectomy" was 0.9 per cent and for "adrenalectomy" 5 per cent. The number surviving thoracolumbar sympathectomy for three to seven years was 73 per cent and for "adrenalectomy" 68 per cent. "Operative mortality" includes those who die in the hospital less than 30 days following an operative procedure. Operative mortality in the adrenalectomy group was influenced by the inclusion of a number of patients who would not have been acceptable for sympathectomy. The common causes of death are stroke, coronary occlusion, uremia, and congestive heart failure (Table VI). Most of the adrenalectomy patients who succumbed died within two years following operation (Table VII). There appeared to be no such pattern among those who died following sympathectomy. The causes of death are those seen commonly among patients with severe hypertension (Table VII) but there are no patients who died with congestive heart failure among the adrenalectomy group.

TABLE V. THE MORTALITY AND SURVIVAL OF PATIENTS WHO HAD "SYMPATHECTOMY" OR "ADRENALECTOMY" THREE TO SEVEN YEARS PREVIOUSLY

	"SYMPATHECTOMY"	"ADRENALECTOMY"
Total patients	114	116
Living	83 (73%)	79 (68%)
Dead (total)	31 (27%)	37 (32%)
Operative mortality*	1 (1%)	6 (5%)

The similarity of the mortality among the two groups of patients is apparent. Early in the series of patients with adrenalectomy, replacement therapy and adequate blood replacement were not as well understood and may have accounted for some of these deaths.

*Survival less than 30 days postoperatively.

TABLE VI. CAUSES OF DEATHS FOLLOWING "SYMPATHECTOMY" OR "ADRENALECTOMY"

	"SYMPATHECTOMY"	"ADRENALECTOMY"
Stroke	15	15
Coronary occlusion	4	12
Uremia	4	4
Congestive heart failure	2	0
Miscellaneous	6	6
Total	31	37

The causes of death are similar in the two groups except that no patient in the adrenalectomy group died from congestive heart failure.

TABLE VII. TIME OF DEATH FOLLOWING OPERATION

YEARS	"SYMPATHECTOMY"	"ADRENALECTOMY"
0-1	8	18
1-2	7	9
2-3	5	4
3-4	5	5
4-5	1	1
5-6	5	0
6-7	-	-
Total	31	37

BLOOD PRESSURE RESPONSE

The blood pressure response has been arbitrarily defined in these patients as one of four groups designated A, B, C, and D (Table VIII). No evaluation of the effect or extent of postural hypotension has been made. A more complete evaluation of the blood pressure changes according to their Smithwick grouping in the surviving patients is presented in Table IX. It is apparent from these data that 37 per cent of the surviving sympathectomy patients and 55 per cent of the adrenalectomy patients had a normal blood pressure after operation and 68 per cent and 80 per cent, respectively, had an A or B response in blood pressure postoperatively. Most of the patients had their operations before the present antihypertensive drugs were available, and subsequently 14 of 19 patients with a sympathectomy have had A or B results while only 5 of 22 patients with adrenalectomy have had further improvement in their blood pressure on depressor therapy. There appears to be little difference in the blood pressure response following either operative procedure among the patients in the Smithwick group IV. However, among the patients in groups II and III of Smithwick's classification, 40 of 62 patients (65 per cent) had an A or B response after "adrenalectomy" while only 31 of 57 patients (56 per cent) had a favorable response to the following sympathectomy. In recent years the liberal use of steroid replacement therapy (usually 25 to 37.5 mg. of cortisone and 2 mg. of DCA or 0.1 mg. of 9-alpha fluorohydrocortisone daily) has probably produced some elevation of blood pressures. Although 32 per cent of our patients after sympathectomy and 21 per cent after "adrenalectomy" have undesirably high blood pressures following operation, almost all have shown

TABLE VIII. DEFINITION OF RESULTS

GROUP	BLOOD PRESSURE	
A	150/100 or less	Supine; equal or less standing
B	150-180/100-110	
C	180-200/110-120	
D	200/120 or more	

This clinical classification has been used in summarizing the response to operation with respect to changes in blood pressure.

TABLE IX. BLOOD PRESSURE* RESPONSE

SMITHWICK GROUP	NO. OF PATIENTS		150		150/100-180/110		180/110-200/120		200/120		NO DATA		DEAD	
	S	A	S	A	S	A	S	A	S	A	S	A	S	A
I	2	0	0	0	0	0	2	0	0	0	0	0	0	0
II	38	31	13	16	11	8	5	1	0	1	3	1	6	4
III	19	31	5	15	2	1	4	1	2	2	4	0	2	12
IV	55	54	9	11	10	10	4	2	7	9	2	1	23	21
Total	114	116	27	42	23	19	15	4	9	12	9	2	31	37
Per cent	100	100	37†	55†	31†	25†	20†	5†	12†	15†	8	2	27	32

Distribution of blood pressure changes in 83 patients surviving "sympathectomy" (S) and 79 patients surviving "adrenalectomy" (A) in relation to the preoperative Smithwick classification of the severity of their hypertension. This table indicates that better blood pressure response is obtained from "adrenalectomy" than from "sympathectomy" but that both procedures will ameliorate the course of the disease even in patients with severe hypertension as characterized by Smithwick groups III and IV.

*Supine blood pressure; equal or less standing.

†Percentages were determined upon the number of patients upon whom data were available three to seven years postoperatively.

some amelioration of symptoms, and signs of vascular damage. Despite persistent hypertension these patients continue for the most part to have good renal function. Following adrenalectomy there were three times as many patients who had coronary occlusion as in the sympathectomy group. Currently, we are studying the blood lipid patterns of our patients before and after operation to see if any correlation can be found to account for this difference.

CARDIAC EFFECTS

The cardiac effects of the operative procedure have been evaluated by several tests. These consist of electrocardiograms and orthodiagrams, as well as the evaluation of symptoms of congestive failure or angina pectoris. In the interpretation of electrocardiograms (Table X) and orthodiagrams (Table XI) four categories have been used: One includes those patients who show definite improvement. A second, designated as the "same," includes patients who had a normal electrocardiogram or orthodiagram prior to the operative procedure as well as patients who had abnormalities which did not improve significantly after their operative procedures. A third group includes those who have shown progressive changes in these studies. The fourth includes those who are known to be alive but upon whom there are no postoperative data available.

TABLE X. ELECTROCARDIOGRAM AFTER OPERATION

SMITHWICK GROUP	IMPROVED		SAME		WORSE		NO DATA	
	S	A	S	A	S	A	S	A
I	0	0	1	0	1	0	0	0
II	11	14	15	10	1	1	5	2
III	7	11	3	5	3	2	4	1
IV	9	23	16	7	2	1	5	2
Total	27	48	35	22	7	4	14	5
Per cent	39*	65*	51*	30*	10*	5*	–	–

Distribution of electrocardiographic changes in 83 patients surviving "sympathectomy" (S) and 79 patients surviving "adrenalectomy" (A) in relation to the preoperative Smithwick classification of the severity of their hypertension. A greater number of patients showed improvement after "adrenalectomy" than after "sympathectomy." The patients classified as "same" include 14 patients in the sympathectomy group and 12 patients in the "adrenalectomy" group who had a normal electrocardiogram before operation as well as those who had an abnormal electrocardiogram and who showed no change in their electrocardiogram after operation.

*Calculation of percentage data was made from those patients on whom follow-up data were available three to seven years after operation.

TABLE XI. HEART SIZE AFTER OPERATION

SMITHWICK GROUP	IMPROVED		SAME		WORSE		NO DATA	
	S	A	S	A	S	A	S	A
I	0	0	2	0	0	0	0	0
II	9	8	14	17	3	0	6	2
III	7	7	6	10	0	0	4	2
IV	8	15	15	15	2	1	7	2
Total	24	30	37	42	5	1	17	6
Per cent	36*	41*	56*	58*	8*	1*	–	–

Distribution of patients according to the changes in their orthodiagrams in 83 patients surviving "sympathectomy" (S) or "adrenalectomy" (A) in relation to the preoperative Smithwick classification of the severity of their hypertension.

*Calculation of percentage data was made from those patients on whom follow-up data were available three to seven years after operation.

Both the sympathectomy and the "adrenalectomy" groups have shown a high percentage of patients who either remain the same or are improved when

evaluated by their electrocardiographic tracings or by their heart size. Among the patients who have shown postoperative improvement with respect to congestive heart failure, it is noteworthy that the "adrenalectomy" group has a significantly higher percentage. Studies by Thorn[6] and Hills[1] would indicate that this may be due in part to the increase in sodium excretion following adrenalectomy. Among the 35 patients who required digitalis for congestive heart failure prior to adrenalectomy, only one still requires digitalis. In the "sympathectomy" group, 19 of 24 patients no longer require digitalis. Improvement of angina pectoris has occurred in 16 of 19 patients after sympathectomy. Three additional patients who had no angina preoperatively developed angina after the operation. After "adrenalectomy," only 2 of 17 patients continued to have angina.

CHANGES IN OCULAR FUNDI

Following either procedure most patients (97.5 per cent) have shown improvement or no progression of the retinopathy (Table XII). In only 2.5 per cent were retinal changes observed to progress. Improvement in the degree of retinopathy has been observed to persist over a long period of time, often when there has been little reduction in the blood pressure.

TABLE XII. OCULAR FUNDI AFTER OPERATION

SMITHWICK GROUP	IMPROVED		SAME		WORSE		NO DATA	
	S	A	S	A	S	A	S	A
I	1		1					
II	15	16	8	4		0	9	7†
III	9	9	3	6	1	0	4	4
IV	17	21	8	3	1	1	6	8
Total	42	46	20	13	2	1	19	19
Per cent	66*	76*	31*	22*	3*	2*	–	–

Distribution of patients according to their hypertensive retinopathy in 83 patients surviving "sympathectomy" (S) or "adrenalectomy" (A) in relation to the preoperative Smithwick classification of the severity of their hypertension. Following either procedure most patients (97.5 per cent) have shown improvement or no progression of the retinopathy. In only 2.5 per cent were retinal changes observed to progress. Improvement in the degree of retinopathy has been observed to persist over a long period of time, often when there has been little reduction in the blood pressure.

*Calculation of percentage data was made from those patients on whom follow-up data were available three to seven years after operation.

†One patient cannot be evaluated because of severe diabetic retinitis proliferans.

RENAL FUNCTION

Blood urea nitrogen and phenolsulfonphthalein excretion determinations have been performed repeatedly. There has been occasional evidence of improvement in renal function. Progressive deterioration has been averted postoperatively in the majority.

OTHER CHANGES

Changes in the cerebral vasculature are difficult to determine without an overt vascular accident. Headaches, however, have been less troublesome in the majority of patients following either operative procedure. In both groups there has been an equal number of cerebral vascular accidents postoperatively. We have attempted to avoid marked fluctuations of blood pressure in patients who may have sclerotic cerebral vessels to prevent cerebral vascular accidents. Hypertensive encephalopathy accompanied by mental changes has improved in some patients in association with improvement in blood pressure.

Postural hypotension has been more persistent among the "sympathectomy" group. Its recurrence more than six months after adrenalectomy is suggestive of impending adrenal insufficiency.[1] Raynaud's phenomena have been observed in both groups of patients during cold weather, but are easily avoided by the use of loose-fitting, warm gloves. A small incidence of peptic ulcer and severe gastrointestinal hemorrhage has been noted in both groups. The effect of steroid therapy upon the incidence and progression of peptic ulceration is being studied in the laboratory animal.[3] Skin pigmentation has been apparent in approximately 30 per cent of those patients having "adrenalectomy." It cannot always be reversed by increasing the steroid replacement.

ADRENAL REPLACEMENT THERAPY

Metabolic studies performed by Hills[1] have indicated that some of the patients who were subjected to subtotal adrenalectomy have shown evidence of sufficient adrenal function to provide minimal support for the patient without exogenous substitution therapy. The average minimal requirement for these patients was 12.4 mg. of cortisone as compared with 32.7 mg. for those who have had total adrenalectomy. In general it has been necessary to continue some exogenous hormone in the patients with subtotal adrenalectomy. Control of adrenal replacement therapy has been relatively easy. There has only rarely been evidence of regeneration of adrenal tissue. Once patients are standardized upon their programs, they require very little change in subsequent months. Recently, in addition to cortisone, 9-alpha-fluorohydrocortisone in dosages of 0.05 to 0.1 mg. daily has been substituted for the 2 mg. of DCA and 3 to 6 Gm. of salt previously recommended. Patients are usually well controlled on 25 to 37.5 mg. of cortisone per day unless they are confronted by situations of acute stress, i.e., infection, fever, or a surgical procedure.

POSTOPERATIVE COMPLICATIONS

A comparison of the postoperative complications shows some differences of morbidity between the two operative procedures (Table XIII). Due to the anatomical relationships in the operation of thoracolumbar sympathectomy, hemothorax and hydrothorax are often encountered as complications. It is evident that adrenal insufficiency was found only in those patients having adrenalectomy. Hemorrhage following the second stage of "sympathectomy" or "adrenalectomy" has been frequent enough to be a serious problem. Persistent postoperative back pain has been a common complaint of most patients following thoracolumbar sympathectomy.

DISCUSSION

There still remain deficiencies in our knowledge of the course of essential hypertension and its amelioration by medical and surgical therapy. Not only are we unable to analyze on a statistical basis the natural course of this disease because of the inability to judge the course of an individual patient or any group of patients, but it is well recognized that the complications of hypertension do not progress in an orderly fashion, well correlated with the blood pressure alone. There is also considerable individual variability in tolerance to the effects of increased blood pressure.

TABLE XIII. POSTOPERATIVE COMPLICATIONS

	S	A
Pleural effusion	69	6
Pneumothorax	31	12
Hemothorax	15	0
Hydropneumothorax	5	1
Pneumohemothorax	10	0
Atelectasis	8	7
Thrombophlebitis	11	8
Pulmonary infarction	3	3
Cerebral vascular accident (nonfatal)	4	11
Fever	2	8
Wound infection	3	16
Adrenal insufficiency (mild)	0	14
Azotemia	6	5
Myocardial infarction	0	3
Pneumonitis	2	3
Retroperitoneal hemorrhage (severe)	0	4
Hemorrhage from wound	0	3
Cardiac arrest	1	0
Empyema	1	0
Hemorrhage from inferior vena cava	0	1
Miscellaneous	19	18
Total	190	123

Complications and sequelae (occurring within 30 days of the operation) in 114 patients (228 operations) after "sympathectomy" (S) and 116 patients (232 operations) after "adrenalectomy" (A). There are fewer postoperative complications following "adrenalectomy."

It is also recognized that in the group of patients with severe hypertension, as characterized by the group IV of the Smithwick classification, there is seldom spontaneous permanent improvement in the blood pressure unless the patient has had a major myocardial infarction or cerebral vascular accident. Many patients in this group have been considered by some to have disease which is too far advanced to be benefited by surgical treatment. While the patients in this group have had the highest mortality in the series reported here, a considerable number have been rehabilitated and most of them have been able to return to their normal occupations. It is a misconception that the adrenalectomized patient on modern drug therapy is an invalid.

"Sympathectomy" and "adrenalectomy" both have been shown to alter the natural courses of severe hypertension and should be considered, as an additional method of treatment, in patients whose hypertension has not been controlled on medical therapy or in those who, irrespective of the degree of control, show evidence of deterioration. It remains a challenge to those interested in the treatment of hypertension by medical therapy alone to show results of a similarly satisfactory nature in patients with comparable severity of the disease. Blood pressure response alone has not been a satisfactory indication of the effectiveness of either operative procedure. While optimally it is desirable to have the blood pressure fall within the normal range, there is considerable evidence that occasionally there is an amelioration of the disease process even with persisting hypertension. In spite of careful study of the routine tests used in preoperative evaluation we have been unable to find any method of predicting which patients will have a satisfactory response following operation, but we have learned that marked impairment of renal function is an absolute contraindication to operation. In our recent experience we have been dismayed

at the increasing number of patients who have been referred for operation too late in the course of their disease, after unsuccessful trials with a variety of vasodepressor agents. It would seem worthy of emphasis that surgical procedures still offer additional help to a considerable number of patients with advanced hypertensive vascular disease in whom medical treatment has failed to halt the progressive pattern of organic damage.

To the best of our knowledge, the results of "sympathectomy" and "adrenalectomy" reported here are better than the results reported following either medical or surgical therapy, for an equally large group of consecutively treated patients with equal severity of disease. A final evaluation of "adrenalectomy" is not possible; however, if over a longer period of time patients continue to have superior postoperative results which justify their need for lifelong adrenal replacement therapy, then it must be concluded that "adrenalectomy" should have a place in the treatment of hypertension. In the meantime it should be recognized that either type of surgical therapy will help the majority of operable patients who have failed to respond satisfactorily to antihypertensive drugs.

SUMMARY

1. A series of 230 patients with severe essential hypertension have been followed for a period of three to seven years after two types of operative procedures. One hundred and sixteen patients had 90 to 100 per cent adrenalectomy and a modified Adson type of sympathectomy. One hundred and fourteen patients had a thoracolumbar sympathectomy. All patients were followed from three to seven years after operation.

2. The criteria for selection of patients for operation are discussed. Poor renal function is the most important single contraindication.

3. The operative mortality was less than 1 per cent for the thoracolumbar sympathectomy series and 5 per cent for those who had an adrenalectomy in addition to some form of sympathectomy. Seventy-three per cent of the patients with thoracolumbar sympathectomy survived during the follow-up period compared with 68 per cent of those having "adrenalectomy."

4. The results of the operations upon blood pressure levels, electrocardiogram, heart size, and ocular fundal changes show superior results following "adrenalectomy." Angina and congestive failure appear to be markedly relieved especially in those patients having "adrenalectomy." Headache was relieved by both operative procedures.

5. The degree to which these patients can be rehabilitated is encouraging.

We wish to acknowledge the facilities made available by Drs. I. S. Ravdin and F. C. Wood and the participation of Drs. C. C. Wolferth, W. T. Fitts, Jr., A. G. Hills, S. B. Langfeld, J. A. Mitchell, and J. Mackie.

REFERENCES

1. Hills, A. G., Zintel, H. A., and Parsons, D. W.: Observations of Human Adrenal Cortical Deficiency, Am. J. Med. 21: 358-379, 1956.
2. Jeffers, W. A., and Zintel, H. A.: Physiologic Problems Related to the Surgery of Hypertension, S. Clin. North America 35: 1629-1644, 1955.
3. Patterson, L., Baret, A. C., Mackie, J. A., Blakemore, W. S., and Ravdin, I. S.: The Effect of Cortisone Upon Peptic Ulceration in the Mann-Williamson Dog. (To be published.)

4. Smithwick, R. H., and Thompson, J. E.: Splanchnicectomy for Essential Hypertension, J. A. M. A. **152**: 1501-1504, 1953.
5. Smithwick, R. H., Bush, R. D., Kinsey, D., and Whitelaw, G. P.: Hypertension and Associated Cardiovascular Disease, J. A. M. A. **160**: 1023-1026, 1956.
6. Thorn, G. W., Harrison, J. H., Merrill, J. P., Criscitiello, M. G., Frawley, T. F., and Finkenstaedt, J. T.: Clinical Studies on Bilateral Complete Adrenalectomy in Patients With Severe Hypertensive Vascular Disease, Ann. Int. Med. **37**: 972-1005, 1952.
7. Wolferth, C. C., Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H., and Hills, A. G.: Effects of Subtotal Adrenalectomy Alone and Combined With Sympathectomy Upon the Blood Pressure Levels and Complications of Severe Arterial Hypertension, Bull. New York Acad. Med. **29**: 115-137, 1953.
8. Zintel, H. A., Mackie, J. A., Sellers, A. M., Jeffers, W. A., Hafkenschiel, J. H., and Lindauer, M. A.: Results of Thoracolumbar Sympathectomy for Essential Hypertension, A. M. A. Arch. Surg. **71**: 215-222, 1955.
9. Zintel, H. A., Wolferth, C. C., Jeffers, W. A., Hafkenschiel, J. H., and Lukens, F. D.: Ninety-five Per Cent Subtotal Adrenalectomy for Essential Hypertension, Surg. Forum, Am. Coll. Surgeons, 1950, Philadelphia, 1951, W. B. Saunders Co., pp. 556-558.

Discussion

DR. KEITH S. GRIMSON (Durham, N. C.).—I would like to congratulate Dr. Zintel and Dr. Blakemore on their trial of adrenalectomy with splanchnicectomy and of splanchnicectomy alone. A small percentage of their patients had angina or cardiac failure before operation. These have not been included in my series of otherwise severe hypertensive patients treated by total sympathectomy including the stellate and celiac ganglia. Extensive removal of the chains and these outlying ganglia minimizes regeneration to thoracic and abdominal viscera. Some vasoconstriction is left to the legs to minimize postural hypotension. It seems worth while to mention the long-term results of "total" sympathectomy for comparison with the two types of splanchnicectomy, with and without adrenalectomy, described by the authors at 3 to 7 years. For 172 patients, our survival rate at 5 years was 81.4 per cent of the patients operated upon, or 84.5 per cent of those surviving operation. The survival rate at 10 to 15 years still exceeds 70 per cent. The authors have referred to reduction of blood pressure on the basis of postural hypotension. Some degree of postural hypotension persists in most of our patients. Most reports emphasize blood pressures obtained in the supine position. Our results at 5 years and later are reduction of supine pressure to normal values in one third, reduction but not to normal in another third, and no reduction except postural hypotension in the remaining third. Patients following "total" sympathectomy have minimal disability and seldom require postoperative treatment. To me at least, the results of "total" sympathectomy have justified its use over any other procedure.

DR. BLAKEMORE (closing).—The discussors have brought out a number of interesting points which time does not permit me to discuss in detail. I would like to thank them, however, for their remarks. It again becomes apparent that there is a great need for a standardization of the classifications for the evaluation of patients with hypertension. It would seem worth while that some national society, such as this one, should designate the present-day most acceptable classification and that all publications should refer to this standard classification. If the authors should desire to use their own classification in addition, they could do so. It is virtually impossible to compare the results of the different surgical procedures from clinic to clinic without such a standard of reference. In the group of patients which we have just presented to this society there are a large number who are in Smithwick's group IV classification, and many surgical groups do not accept for operation patients with hypertension of this severity. We feel that it is worth while to do so, and a significant number of these patients have been rehabilitated following the operative procedure. Survival of adrenal tissue in the patients who had subtotal adrenalectomy has been studied by Hills,[1] and we have found no evidence of progressive regeneration. There is, however, a significantly lower steroid requirement in those patients who have been left with a remnant of adrenal tissue.

THE VICIOUS CIRCLE IN HYPERTENSION

Its Surgical Significance

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INTRODUCTION AND PURPOSE OF STUDY

IN A previous report[1] a group of 250 hypertensive patients, operated on between 1934 and 1946, were studied. The follow-up of these patients was of comparatively short duration, i.e., from one to six years, and the grading of the severity of hypertension was into three groups which was a simplification of the basic grouping used by Keith, Wagener, and Barker.[2] The three groups of essential hypertension used for an indication of operability were as follows:

Group I. Age below 40 years; some detectable organic damage; normal blood pressure on complete rest or barbiturates; casual diastolic pressures above 100 mm. Hg.

Group II. Age from 20 to 55 years; moderate vascular sclerosis in several organs; diastolic pressure irreducible below 110 mm. Hg by any method; rising diastolic pressure in spite of skillful medical management.

Group III. Retinal hemorrhage, exudate or papilledema; high fixed diastolic pressure, which cannot be lowered by any means; congestive or anginal heart failure, but not in the last three months; cerebrovascular accidents but at least three months ago, without much crippling; an accelerated phase of hypertension but with fair renal function.

There have been many attempts at grading the severity of hypertension.[3] No one can readily give the hypertensive patients with their various hereditary backgrounds, their recurrent forms of stress, and their degrees of organic vascular damage a simple numerical figure so as to be comparable with other groups treated nonsurgically. Then again, the impressive survival rates of surgically versus nonsurgically treated patients[3c] can be hardly valid today, when hypotensive drugs are so widely and successfully used, undoubtedly prolonging the life of the nonsurgical hypertensive.[4]

Added to these difficulties of evaluating the surgical therapy of hypertension is the fact that most hypertensives today, whether postsurgical or nonsurgical, and whether they need it or not, are on some form of drug therapy so that a long-term follow-up will have to deal with a combined effect of drugs, diet, and operation.

In spite of these obvious hurdles a re-examination of patients operated on between 1934 and 1946 was undertaken; no one operated on less than ten years

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ago was included, although in a report made five years ago[5] our material had risen to 562 patients and is being regularly followed year after year.*

Criteria of Operability.—Ever since the first case, done in 1934, extreme conservatism was observed, and hence our very low operative mortality and morbidity. Only two deaths were encountered in this group, both deaths occurring during anesthesia by inexperienced personnel, and not on either of the two vascular services under our supervision. The indications have already been mentioned in the previous section of this paper. Attention has been called to the fact again and again in our earlier papers,[5] that the renal factor is the limiting factor of operability, and beyond a certain stage of renal impairment, splanchnicectomy has been of no avail. Arbitrarily a 15-minute phenolsulfonephthalein excretion below 15 per cent and a specific gravity of concentrated urine below 1.016 have been regarded as contraindications to operation, and so has a certain degree of personality disorder in the presence of which a postoperative psychosis may develop.[6] Cardiac failure, previous coronary or cerebrovascular accident have not been regarded as contraindications.

The Concept of the Vicious Circle.[7]—This concept, first enunciated by Franz Volhard[7a] in 1931, and re-emphasized on the basis of their animal experiments by Byrom and Dodson,[7c] is based on the observation that a unilateral renal hypertension, after having persisted for some time, will adversely affect the function of the remaining kidney in inflicting hypertensive arteriolar sclerosis upon it. But it has a far wider applicability than this. A neurogenic hypertension will become secondarily renal and a renal hypertension will develop neurogenic characteristics by an increased vascular reactivity. Both renal and neurogenic hypertensions will secondarily produce corticoadrenal activity and a primary pheochromocytoma or a corticoadrenal adenoma will develop neurogenic and renal characteristics. All three of these modalities will affect the homeostatic mechanism of the baroceptors, and increased firing of depressor impulses from the carotid artery can be measured.[8] The vascular system once subjected to a prolonged rise in blood pressure has lost its normal blood pressure regulation—perhaps through changes in the wall of the aortic-carotid vessels.

Elsewhere, one of us (G. de T.) has described in detail how various factors in human diastolic hypertension can be evaluated.[5] Here we can simply state that reduction of diastolic hypertension is an urgent matter and that the intermittent lowering of pressure by drugs with throttling of some physiologic mechanisms may transform the hypertension to a more intractable one.

The object of therapy then would be to eliminate the primary cause of hypertension by attacking the neurogenic, renal, or adrenal mechanism. Should the vicious circle be in full force, surgery can still break the circle at critical points, at renal or adrenal levels.

Material Studied.—A total of 105 patients were available, operated on between 1934 and 1946 at St. Luke's Hospital and the Research and Educational Hospitals. Because of lack of sufficient data the group operated on at the Veterans Facility is not included in this series (Table I). Of the 105 patients,

*The total number of records now exceeds 600. The expense of re-examination and social service work was borne by a special fund available to the senior author through an accumulation of Grants for Clinical Research at St. Luke's Hospital.

85 are available for study; of the 20 who died, 6 died of other than cardiovascular causes, 2 of unknown cause, which left 12 patients who died of cardiovascular-renal disease.

TABLE I. ANALYSIS OF POSTOPERATIVE FOLLOW-UP (1934-1946) OF PATIENTS OPERATED ON FOR DIASTOLIC HYPERTENSION

Patients traced	105
Patients died	20 (19%)
Available for study	85

METHODS OF STUDY

A questionnaire, more detailed than the ones used previously, was mailed out, and an effort was made to reach those whose address was unknown, by inquiry to their employers or their neighbors.* The summary sheet of their preoperative work-up represented here in its latest modification was restudied (Table II). In addition, a severity index was determined, based on the preoperative status of the patient according to criteria shown in Table III. While

TABLE II. SUMMARY SHEET OF HYPERTENSIVE WORK-UP

(NOTE: PATIENT SHOULD ARRIVE BEFORE 5:00 P.M.)

ORDERS*

Date: ----------: Night of admission:
(1) Select, high-vitamin, high-protein diet
(2) 6:00 P.M.: Concentration and dilution test starts

Date: ----------: First Day:
(1) CBC, Hgb., differential, and hematocrit
(2) Urinalysis
(3) Sedimentation rate
(4) Kahn
(5) Blood pressure every 4 hours day and night by nurse during entire study
(6) Blood for typing
(7) Blood chemistry: BUN, NPN, cholesterol, sugar
(8) Electrocardiogram in afternoon
(9) P.S.P. tests in afternoon
(10) Consultation with ophthalmologists: Dr. ----------
(11) Consultation with internist: Dr. ----------
(12) Interview with social worker

Date: ----------: Second Day:
(1) Urea clearance test
(2) Insulin tolerance test—*if ordered*
(3) Sodium Amytal test in afternoon
(4) *No* castor oil—as preparation for I.V.P.
(5) Special tests to be done by intern in the afternoon
  (a) Cold pressor test
  (b) Postural pressor test
  (c) Tourniquet test

Date: ----------: Third and Fourth Days:
(1) Basal metabolic rate
(2) Two-meter chest plate in morning
(3) Intravenous pyelogram in afternoon with prostigmin amp. 1, 1:2000
(4) Etamon test
(5) Glucose tolerance test—*if ordered*
(6) Histamine test—*if ordered*
(7) Regitine test—*if ordered*
(8) ACTH—eosinophilia—*if ordered*
(9) Aortogram—*if ordered*

Note: Notify Service Immediately if Any Test Is Not Completed According to Instructions.

*See Instruction Sheet for carrying out tests.

*Miss Mildred A. Bomba, R.N., of the Social Service Department, rendered a most helpful service.

TABLE III. SEVERITY INDEX OF DIASTOLIC HYPERTENSION

PANELS	GRADES			
	1	2	3	4
Diastolic pressure (in mm. Hg)	95-110	111-125	126-140	<140
Cardiac function	Early myocardial change; slight enlargement	Marked myocardial damage; heart over 50 per cent. Cardiac thoracic ratio	Angina or controlled compensation	Coronary occlusion; congestive heart failure
Renal function (15′ P.S.P. in per cent)	35-25	24-20	19-15	14-10
Cerebral involvement	0	Severe hypertensive headache	Old stroke	Fresh stroke or encephalopathy
Eye grounds	Narrowing or spasm	A.V. nicking and much sclerosis	Hemorrhage and exudates	Papilledema

in our previous studies we paid a great deal of attention to the cardiac, renal, and retinal status, it seemed important to establish a separate panel for cerebral involvement since retinal and cerebral involvement by no means parallel each other. In addition, the level of diastolic pressure, which has such an important bearing on vasospasm,[9] seems to have an important bearing on prognosis, so that numerical values were attached to it. Thus the original three groups, which have remained unchanged since the start of our surgical activities, could now be redefined in the following manner:

1. Intermittent hypertension with early vascular damage in eye grounds, brain, heart, or kidney has a severity index from 3 to 8.

2. Rising diastolic pressure in middle-aged hypertensives in spite of adequate medical care has a severity index from 9 to 12.

3. Rapidly progressive premalignant or malignant hypertension but adequate renal function not below 15 per cent P.S.P. excretion in 15 minutes has a severity index from 12 to 17.

No operations were advised or carried out on (1) adolescent or juvenile hypertensives with no detectable vascular damage, (2) patients whose diastolic pressure was stable at 110 to 120 mm. Hg with a high pulse pressure on skillful medical care, and (3) patients in the malignant phase with nitrogenous retention, hypertensive encephalopathy, no concentrating ability above 1.015 or less than 15 per cent P.S.P. excretion.

EVALUATION OF RESULTS

Since the operation, 20 out of the 105 patients died, a mortality rate of 19 per cent (Table I). This is a comparatively low mortality rate compared with a graph published by us previously[5] (Fig. 1). Obviously this collected material[10] varies greatly in severity from the advanced premalignant and malignant cases of Norman Keith to the ambulatory patients in Perera's hypertension clinic. Furthermore, six of our patients died from other than cardiovascular-renal disease.

For the remaining 85 patients, we have compared their preoperative hypertensive status based on the original grouping and the severity index with their

present state obtained either by personal interview and laboratory studies or through cooperation with their attending physician (Table IV). Naturally not all data are available on everyone, but in addition to the symptomatic improvement, a concentration test, an electrocardiogram, a 2-meter chest film, and a nonprotein nitrogen determination were always obtained. While one of us, (W. H. H.) graded the preoperative indices, another surveyed the postoperative ones (G. de T.), so that bias could be kept to a minimum. The results of this survey are shown in Fig. 2.

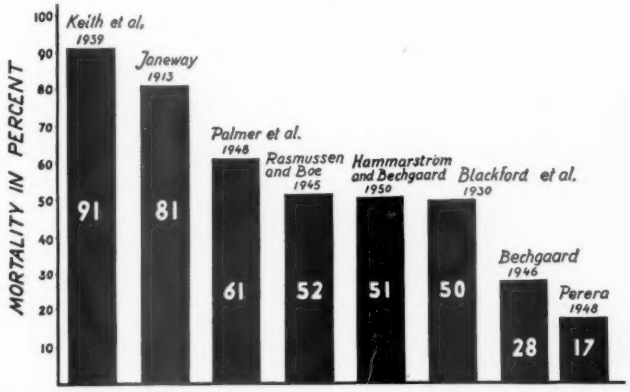

Fig. 1.—Mortality among hypertensive patients not treated surgically. (Reconstructed from Smithwick.[10])

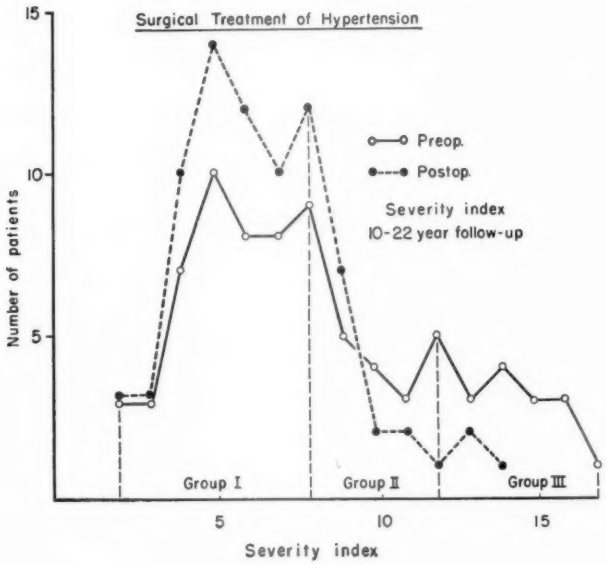

Fig. 2.

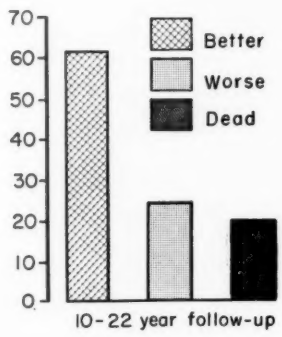

Fig. 3.

Fig. 2.—Pre- and postoperative severity indices in 79 hypertensive patients. Note that the severity of hypertension shifts to the left after operation, indicating an over-all reduction of severity.

Fig. 3.—End result of surgical treatment for hypertension after ten to twenty-two years.

In the group of 79 patients with usable preoperative and postoperative data, the severity indices shifted toward the left, indicating that, for the total group, hypertension was less severe 10 to 22 years after operation than before

TABLE IV. FOLLOW-UP QUESTIONNAIRE FOR PATIENTS OPERATED ON FOR HYPERTENSION

NAME _____ DATE _____
ADDRESS _____

1. Compare the following symptoms you now have with your symptoms before surgery by checking the appropriate square. Have the following symptoms been:

	Relieved	*Unchanged*	*Improved*		*Worse*
			Slightly	Markedly	
A. Headaches					
B. Nervousness					
C. Fatigue					
D. Palpitation					
E. Shortness of breath					
F. Chest pain					
G. Nosebleeds					
H. Ankle and foot swelling					
I. Urinary frequency					

2. What is your blood pressure after five minutes in the following positions:
   Horizontal: _____ Sitting: _____ Standing: _____
3. What is the specific gravity of your urine? _____
   Do not drink any fluid after 6:00 P.M. the night before. Collect the entire specimen of urine you void after first arising in the morning.
4. Are you working? Yes _____ No _____ Full time _____
   Part time _____ How many hours per week _____ Type of job _____ (If housewife, so state)
   If not working, is this due to the state of your health? _____
5. Do you feel your daily activity is: Normal _____
   Limited because of your health _____
6. Have you had any of the following blood chemistry studies performed during the past year? If so, we would like the results.
   N.P.N.
   B.U.N.
   P.S.P. kidney function test
7. Has an electrocardiogram (ECG) been taken during the past year? If so, could you send us the ECG tracing as well as the report?
8. Has a chest x-ray been taken during the past year? We are interested in the heart size. Could you send us the x-ray report of the heart size measurement?
9. Is there anything else you can tell us about your health? Have you had any illnesses since your surgery for hypertension?
10. Do you feel your general health and well-being is:
    Excellent _____ Good _____ Fair _____ Poor _____

operation. In the group of patients with indices from 10 to 17, there has been a definite improvement, and this represents the late group 2 and group 3 hypertensives. Since such a frequency polygon does not reveal improvement of the individual but of the whole group, we have compared the severity indices of the individual before and after operation. Sixty-one patients had lower indices, 24 patients had higher indices, and 20 died (Fig. 3).

There are too few patients in this group to allow for further subdivisions, but, as has been repeatedly shown particularly by Smithwick,[3c] women always do better than men, and, as Fowler and I have shown, the "renal" type of hypertension has done better than the "neurogenic."[11] We shall refer to this paradox in the discussion (Table V).

It would appear, then, that over a period of 10 to 22 years, roughly 60 per cent of hypertensives have maintained an improvement (Table VI). Subjective symptoms, especially headache, have been relieved in three-fourths of

the patients. Fatigue seems to be the most persistent symptom but, of course, is difficult to interpret. Palpitation, shortness of breath, and chest pain—symptoms of functional or organic cardiac involvement—have been relieved in 60 per cent of the patients. Ankle and foot swelling and urinary frequency have not been symptoms of the nephrosclerotic patients except terminally. They occurred in 20 per cent of all patients before and after operation. Electrocardiogram and heart size improved in 51 and 47 per cent, respectively. We have been impressed with the lack of correlation between the objective and overall subjective improvement, since 62 per cent of the patients who survived the ten- to twenty-two-year period stated that they felt *fair*. We have no comparisons to make between nonhypertensive population groups of the same age and sex, but the cross section of the middle-aged metropolitan population seems to feel "fair" when questioned professionally, not socially.

TABLE V. CLASSIFICATION OF PATIENTS OPERATED ON FOR DIASTOLIC HYPERTENSION (1934-1946)

"Essential" hypertension	71
Primary renal disease	31
Corticoadrenal adenoma	2
Coarctation of the Aorta	1
Total	105

TABLE VI. IMPROVEMENT FOLLOWING SURGICAL TREATMENT FOR HYPERTENSION

SYMPTOM OR SIGN	IMPROVEMENT IN PER CENT
Headache	75
Palpitation, Dyspnea, Angina, Ankle edema	60
Urinary frequency	--
Electrocardiogram	51
Heart size	47

Since blood pressure, concentration test in an overnight specimen, and working ability were three simple criteria to be readily obtained at an office visit on all patients, we were interested in comparing these data with the strict criteria of the severity index. The electrocardiogram and the high normal nonprotein nitrogen put many patients in a more severe grade than would have been suspected by their clinical status.

DISCUSSION

The difficulty of evaluating the results of surgical procedures for hypertension is obvious. But when the causes of failure are studied, as has been done in a previous communication,[6] one important point stands out which has had only occasional and all too limited emphasis.[7] It involves the concept of a vicious circle in hypertension, which occurs, for instance, in a unilateral renal hypertension in the opposite originally uninvolved kidney. This kidney then, because of hypertensive vascular damage, becomes a source of hypertension

which is not reduced by removing the original source. A neurogenic hypertension, in our experience, responds well to splanchnicectomy but not when secondary renal damage has become an irreversible factor. The residual hypertension, after elimination of coarctation of the aorta, pheochromocytoma, or corticoadrenal tumor, could originate in nephrosclerosis, but we, like others,[12] have failed to always find renal damage, so that a neurogenic or vascular damage with baroceptor disturbance is detectable.

It is important, then, to eliminate the primary source of hypertension before secondary mechanisms have come into play. In our mind, the neurogenic and corticoadrenal forms are suitable for early surgical therapy. The real problem today is that of the renal hypertension. Except for energetic antibiotic therapy for chronic pyelonephritis, medical management has not been able to prevent progressive renal involvement terminating in uremia.

In a previous study of mine with Fowler,[11] it was pointed out that the renal origin of hypertension by no means contraindicates sympathectomy. On the contrary, some of our best results were obtained in patients who suffered one or two bouts of toxemia of pregnancy or had a microscopically verified atrophic pyelonephritis or postscarlatinal nephritis. The acute disease was arrested, with residual arteriolar or arterial damage and infarcts. Increased vascularity to the kidney reduced hypertension, but unless this was done *early*, within a few years of the inception of the disease, secondary vascular damage due to persistent hypertension vitiated the results.

The idea that sympathectomy cannot improve decreased renal function is correct in so far as it relates to excretory function and to a basal state. We have never seen a diminished urea clearance, a concentration-dilution test, or phenosulfonephthalein test improve after sympathectomy. As pointed out by Homer Smith[13] in his classic monograph on the kidney, renal plasma flow is often reduced in hypertension but in glomerulonephritis the renal plasma flow may be greatly reduced without hypertension. There is then diffuse parenchymal renal disease both in pyelonephritis and in glomerulonephritis without hypertension. What is the factor which appears in hypertension?

The striking histologic studies of Priscilla Kinkaid-Smith[14] are pertinent here. Pyelonephritis only caused hypertension when the inflammatory reaction produced vascular obstruction or incomplete infarction. Such lesions seem amenable to sympathectomy.

The severe benign nephrosclerosis, on the other hand, is unaffected, and in this group a revascularization of the ischemic kidney has been attempted by Scupham and one of us (G. de T.) by decapsulation and scarification of the kidney followed by implantation of muscle or omental flaps.[15] The course of one such case is presented in Fig. 4. One notes that the severe hypertension, with a severity index of 13, was kept stationary for 56 months. Six years after nephro-omentopexy, the patient died of a stroke. A history of a rapidly progressive hypertensive of at least four years' duration was elicited. Whether earlier cases would fare better has not been determined. In another case at autopsy marked capillary and venous dilatations were seen at the junction of omentum and kidney.

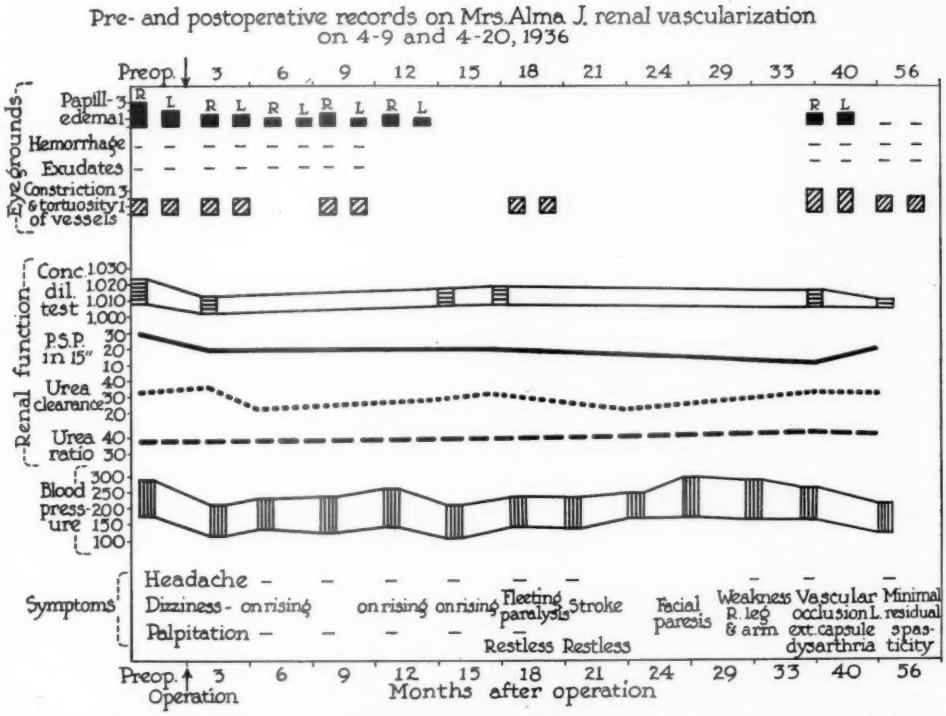

Fig. 4.—This patient was judged unsuitable for splanchnicectomy. She died six years later of a stroke, but not uremia. (From de Takats and Scupham: Arch. Surg. **41**: 1394, 1940.)

Fig. 5.—Note the obstruction at the origin of the left renal artery. The left kidney is poorly vascularized and showed poor renal function. (Courtesy Dr. W. S. Dye.)

We have also been looking for renal arterial obstructions, and one such aortogram is shown in Fig. 5. This patient had a severe progressive hypertension with poor renal function on the left side. Only recently, a patient died on our service from a massive intracerebral hemorrhage. In spite of intravenous and retrograde pyelograms and split renal function tests, the hypoplastic infarcted left kidney could not be identified preoperatively. With the help of a modified type of aortography, Humphries has detected and surgically attacked six cases.[16]

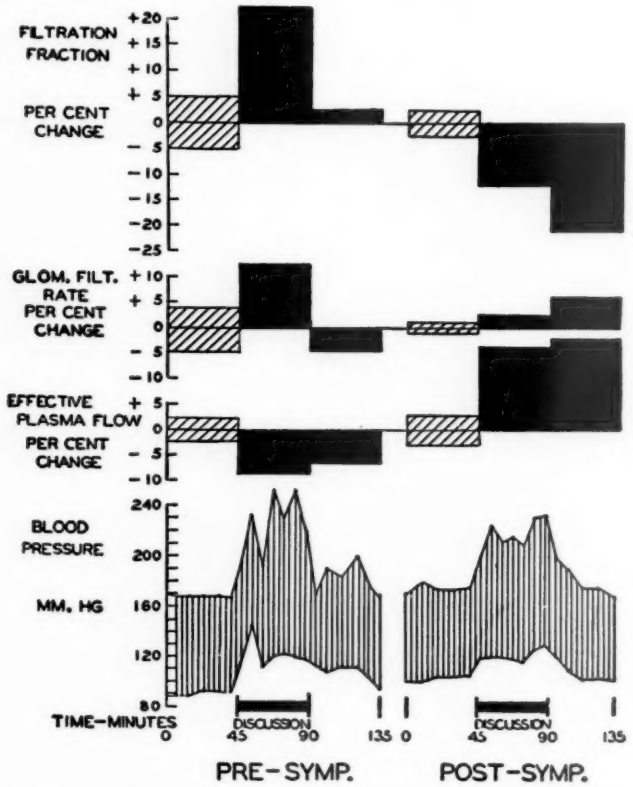

Fig. 6.—Changes in blood pressure and renal hemodynamics during a stressful interview, before and after bilateral thoracolumbar sympathectomy. Note the postoperative *increase* in effective plasma flow owing to decreased renal vascular resistance. (Courtesy Wolf, Cardon, Shepard, and Wolff: Life Stress and Essential Hypertension, Baltimore, 1955, The Williams & Wilkins Co.

It seems, however, that splanchnicectomy itself is often capable of breaking the vicious circle, since not only does it eliminate sudden overshoots of pressure which follow exertion, the Valsalva experiment, and central vasospastic impulses, but it abolishes fluctuations of renal blood flow and function due to emotional stimuli, posture, pain, and cold (Fig. 6). Denervation of the adrenal gland, effected by sympathectomy, shows histologic changes not only in the medulla but also in the cortex. The late Dr. R. H. Jaffe, pathologist at Cook County Hospital, studied the denervated adrenal glands of dogs for us and reported marked accumulation of sudanophil material.[17] A homogeneous appearance of the three zones of glomerulosa, fasciculata, and reticularis was reported by Weidemann,[18] and recently Etienne-Martin[19] has expressed the thought that the entire adrenal gland is influenced by sympathectomy.

Splanchnicectomy has been then our key procedure to break the vicious circle in hypertension. Added to this operation, however, are pedicled flaps of muscle to the kidney whenever a renal biopsy was taken and partial adrenalectomy when the salt-retaining factor was especially prominent. In retrospect, two cases of aldosteronism are in this series, in one of which a cortical adenoma was removed (Fig. 7). What the muscle flap in the scarified kidney can produce in a way of increased vascularity is not subject to proof in this series. However, in the animal experiment, Baronofsky[20] and his associates showed that the small intestine with its mesenteric blood supply is capable of bringing functioning anastomoses to an ischemic kidney.

Fig. 7.—Cortical adenoma in a patient showing water retention and hypochloremic alkalosis. (From de Takats and Fowler: Am. Heart J. 38: 234, 1949.)

SUMMARY

In a group of 105 hypertensive patients available for study from ten to twenty-two years after their surgical treatment, 61 had improved, 24 had progressed to a more severe state, and 20 died. In addition to a simple grading into three groups, a severity index was established on the basis of diastolic pressure, cardiac status, renal function, cerebrovascular involvement, and eye grounds. Seventy-nine patients could be re-examined by the same criteria. The over-all severity of the total group was definitely decreased compared to their preoperative status.

While the primary cause of "essential" hypertension, whether neurogenic, endocrine, or renal is not always obvious, an early direct attack on the primary cause interrupts the vicious circle, during which secondary mechanisms come into play. Even here splanchnicectomy may play a role in influencing corticoadrenal activity and renal blood flow. Adrenalectomy or renal vascularization has a small, definite indication. Segmental renal arterial obstructions are amenable to surgical correction.

REFERENCES

1. de Takats, G., Julian, O. C., and Fowler, E. F.: The Surgical Treatment of Essential Hypertension. IV. Case Selection and Technique as Influencing Results, SURGERY **24**: 469, 1948.
2. Keith, N. H., Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension, Their Course and Prognosis, Am. J. M. Sc. **197**: 332, 1939.
3. (a) Peet, M. M., and Isberg, E. M.: Surgical Treatment of Arterial Hypertension, J. A. M. A. **130**: 467, 1946. (b) Hinton, W. J., and Lord, J.: Analysis of Surgical Failures and Fatalities Following Thoracolumbar Sympathectomy for Essential Hypertension, New York J. Med. **46**: 1715, 1946. (c) Smithwick, R. M., Bush, R. D., and Kinsey, D.: Hypertension and Associated Cardiovascular Disease, J. A. M. A. **160**: 1023, 1956. (d) Corcoran, A. C., Dustan, H. D., Taylor, R. D., and Page, I. H.: Management of Hypertensive Disease, Am. J. Med. **17**: 383, 1954.
4. Schroeder, H. A., and Perry, H. M.: Current Status of Therapy in Hypertension, J. A. M. A. **162**: 1382, 1956.
5. de Takats, G.: Limitations of Sympathectomy in the Treatment of Diastolic Hypertension, J. A. M. A. **148**: 1382, 1952.
6. de Takats, G.: Causes of Failure in the Surgical Treatment of Hypertension, Angiology **1**: 547, 1950.
7. (a) Volhard, F., and Fahr, T.: Nieren und Ableitende Harnwege. *In* Bergmann and Stahelin: Handbuch der Inneren Medizin, Berlin, 1931, Gustav Springer, Vol. 6, Part 1. (b) Wilson, L., and Byrom, F. B.: The Vicious Circle in Chronic Bright's Disease. Experimental Evidence From the Hypertensive Rat, Quart. J. Med. (N.S.) **10**: 65, 1941. (c) Byrom, F. B., and Dodson, L. F.: The Mechanism of the Vicious Circle in Chronic Hypertension, Clin. Sc. **8**: 1, 1949.
8. Green, J. M.: The Blood Baroceptor Control of Blood Pressure, Proc. Council for High Blood Pressure Res. **3**: 39, 1954.
9. Byrom, F. B.: The Pathogenesis of Hypertensive Encephalopathy and Its Relation to the Malignant Phase of Hypertension. Experimental Evidence From the Hypertensive Rat, Lancet **2**: 201, 1954.
10. Smithwick, R. M.: Surgical Measures in Hypertension, Springfield, Ill., 1951, Charles C Thomas.
11. de Takats, G., and Fowler, E. F.: Surgical Treatment of Hypertension: Neurogenic Versus Renal Hypertension From the Standpoint of Operability, SURGERY **21**: 773, 1947.
12. Pickering, G. W.: High Blood Pressure, New York, 1955, Grune & Stratton, Inc.
13. Smith, H.: The Kidney. Structure and Function in Health and Disease, New York, 1951, Oxford University Press.
14. Kinkaid-Smith, P.: Vascular Obstruction in Chronic Pyelonephritic Kidneys, Lancet **2**: 1263, 1955.
15. de Takats, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, Arch. Surg. **41**: 1394, 1940.
16. Humphries, A. W. Personal communication.
17. de Takats, G., and Cuthbert, F. P.: The Effect of Suprarenal Denervation and Splanchnic Section of Sugar Tolerance of Dogs, Arch. Surg. **3**: 151, 1935.
18. Weidemann, W.: Auswirkungen der lumbalen Sympathectomie auf den Gesamtorganismus, besonders auf Hoden und Nebennieren, Zentralbl. Chir. **77**: 1385, 1952.
19. Etienne-Martin, P.: A Study of Adrenal Insufficiency After Treatment of Hypertension by Bilateral Sympathectomy Plus Unilateral Adrenalectomy, Ciba Foundation Symposium on Hypertension, Boston, 1954, Little, Brown & Co.
20. Katz, Y. J., Hannon, D. W., Alden, J. F., and Baronofsky, I. D.: The Revascularization of the Kidney, SURGERY **39**: 623, 1956.

STUDIES OF SYMPATHETIC DENERVATION OF THE FOREPAWS IN UNANESTHETIZED DOGS

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THE relapse of symptoms following sympathectomy of the upper limb for vascular disorders is far more common than after sympathetic denervation of the lower limb.[4, 12, 41, 42] Many theories have been offered to explain vasomotor recovery following sympathectomy: development of intrinsic vascular tone,[5, 18] hypersensitivity of the denervated vessels,[2, 6, 13] regeneration,[19, 20, 25, 31] "reorganization,"[15] and incomplete denervation.[1, 27, 36] However, the explanation for the difference between the results of upper and lower limb sympathectomy remains uncertain.

This study was designed to provide data which may help to evaluate at least one of the factors that may be responsible for this difference, namely, incomplete denervation. Measurements of the circulation in the forepaws of dogs were undertaken following purposely incomplete denervations, as well as following supposedly complete denervations, to find out whether or not there were any characteristic features of the results of incomplete denervation which would help to identify this factor in cases of relapse following sympathectomy.

METHOD OF STUDY

Dogs were trained to permit measurements of the peripheral circulation in the conscious state, as it has been shown that anesthesia itself inhibits vasomotor tone in the extremities.[23] Observations were made in a controlled temperature room with the ambient temperature maintained at 20° C. and the humidity constant. It was also found necessary to clip the animals' hair to permit cooling of the skin to a level approaching the ambient temperature. After one hour in the room, measurements were made of the interdigital skin temperature and the skin temperature of the ear with iron constantan thermocouples and an automatic recording potentiometer. Blood flow through the forepaws was measured by venous occlusion plethysmography, using volume transducers and a direct writing oscillograph.

Six mongrel dogs of both sexes, weighing 10 to 15 kilograms, were selected and trained for a period of 2 to 4 weeks. Basal studies were carried out 8 to 10 times on each dog before operation.

The sympathetic innervation of the dog's forelimb has not been studied as thoroughly as in other animals, but the preganglionic outflow is said to arise mainly from the fourth to the ninth dorsal segments.[29] This coincides fairly

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closely with descriptions that have been given for the cat,[16, 29] monkey,[16, 37] and man,[14] although Kuntz and associates[28] have found significant contributions from as high as the first dorsal segment, both in these animals and in man. It is generally agreed that the postganglionic fibers arise from the stellate ganglion.

Accordingly, a forelimb sympathectomy, presumably complete, was performed in each dog by resecting the thoracic sympathetic trunk from the stellate to the tenth ganglion inclusive. Following operation, measurements of the skin temperatures and blood flows were carried out daily for the first postoperative week, every other day for the second week, and then less frequently as the values became stabilized.

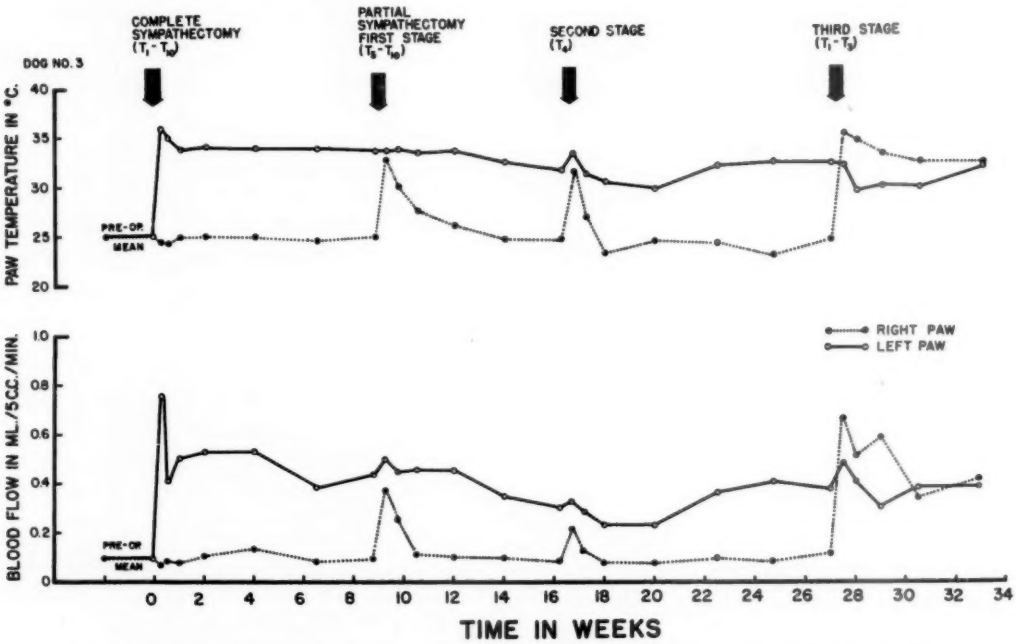

Fig. 1.—Graph showing typical results following complete and partial denervations. Each point plotted after first postoperative values represents mean of 2 to 4 consecutive measurements.

After 8 weeks had elapsed, an operation was performed on the contralateral side to achieve partial denervation of the paw by resection of the fifth to the tenth thoracic ganglia inclusive. Similar postoperative measurements were carried out. Eight weeks later the partial denervations were extended by the removal of a single extra ganglion, the fourth, which should now have made division of the preganglionic outflow complete. Measurements of the circulation were continued for a further 8 weeks, at which time the partial sympathectomies were extended to include the stellate ganglion, as on the contralateral side which had been made "complete" at the outset. Finally, at the end of the study, exploration of the lower cervical sympathetic trunk was carried out in one dog which had developed complete return of vasomotor activity after the above procedures.

RESULTS

Complete Sympathetic Denervation of the Forepaw.—Following complete denervation from the stellate to the tenth thoracic ganglia, the immediate results

were as follows. (1) The denervated paw showed an initial rise in blood flow to approximately 5 times the control values, with an increase in interdigital skin temperature of 10 to 12° C. (Figs. 1-3). (2) An ipsilateral Horner's syndrome was produced in each dog, accompanied by vasodilatation in the ear, with

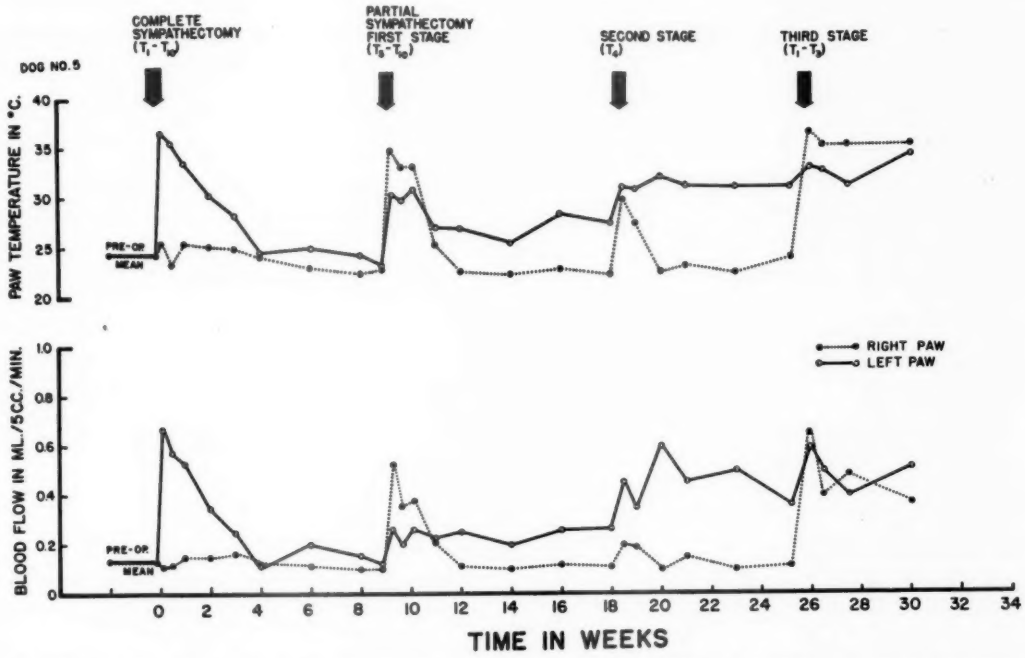

Fig. 2.—Graph showing early recovery of vasoconstrictor activity following complete sympathectomy, with release of this activity after contralateral denervation.

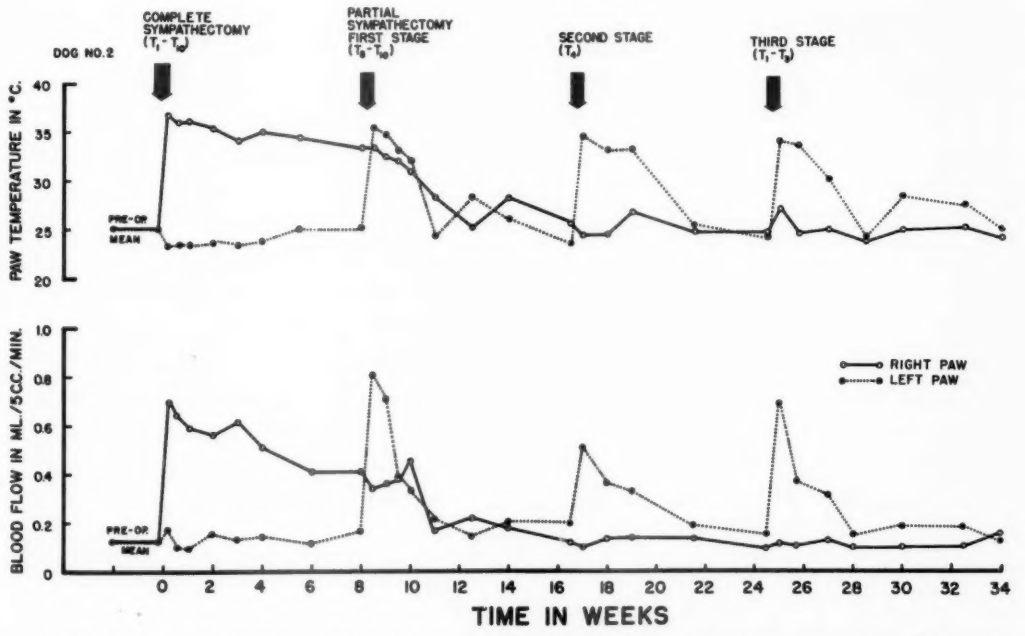

Fig. 3.—Graph showing delayed return of vasoconstrictor activity after complete sympathectomy. Note that immediate response of partial denervation is indistinguishable from complete denervation.

an increase of about 10° C. in the skin temperature of the ear. (3) No change was observed in the circulation of the normally innervated contralateral paw.

Beginning the next day and continuing for the next 5 to 8 days, the initial vasodilatation subsided noticeably, with a marked reduction in blood flow but a lesser decrease in skin temperature. In the succeeding 8 weeks before the next operations, all but 2 of the dogs maintained an increase in blood flow 2 to 4 times greater than that of the normally innervated paw, together with an increase in interdigital skin temperature of 8 to 10° C. (Fig. 1).

Two of the dogs, however, showed an early return of vasomotor activity in the supposedly completely denervated paws. In these 2 animals, within 3 weeks, the circulation of the denervated paw was indistinguishable from that of the contralateral control paw (Fig. 2). This early return of vasomotor control in these 2 dogs is particularly significant in relation to the results of the contralateral incomplete denervations which will be described later, for it proved to be due to innervation crossing from the opposite sides. When ganglionectomy was undertaken on the contralateral sides, both of these animals showed a new release of vasoconstrictor tone which was sustained for the remaining 10 weeks of the study (Fig. 2).

One dog showed return of vasoconstrictor activity 10 weeks after the initial complete denervation on the right side and also showed a prompt return on the contralateral (left) side after it had been completed by resection of the stellate ganglion (Fig. 3). This was the only animal to show disappearance of the Horner's syndrome on the side of the complete denervation with a return of vasoconstriction in the ipsilateral ear. In this dog exploration of the lower cervical sympathetic trunk was carried out on the right side, with resection of the lower cervical sympathetic trunk and the caudal cervical ganglion of the combined vagosympathetic trunk. This operation was followed by a new release of vasoconstrictor tone in both forepaws. As this was the final operative procedure, insufficient time has elapsed to show how long this will be sustained.

Incomplete Sympathetic Denervations of the Forepaw.—The results of the incomplete denervations of the contralateral paws were as follows. (1) The first partial denervations produced results ranging from slight vasodilatation in 2 animals (Fig. 1) to a large increase in blood flow and skin temperature in the other 4, indistinguishable from that following complete sympathectomy (Figs. 2 and 3). (2) Beginning the second to the fifth postoperative day, return of vasomotor activity occurred in every instance and was complete within 3 weeks or less. (3) Resection of an additional ganglion, the fourth, was followed by a new release of vasoconstrictor activity identical to that following complete sympathectomy in 3 animals but with a less marked vasodilatation in the other 3. The subsequent course was similar to the previous partial denervations with the same quick return of vasomotor activity, showing that there remained a significant residual innervation above the level of the fourth ganglion.

Resection of the stellate ganglion to complete the denervations was followed by loss of vasomotor control which was maintained for the final weeks of the study in every dog but one (Fig. 3) which has already been described.

It is interesting to note that on several occasions the initial postoperative vasodilatation was accompanied by a transient reduction in blood flow in the opposite paw—probably due to the phenomenon of blood shift or "hemometakinesia" described by DeBakey and co-workers.[8]

DISCUSSION

Review of the literature suggests that animal experiment would be unrewarding in evaluating clinical problems of sympathectomy for vascular disease in man, for it is widely stated that the increase in blood flow following sympathectomy in animals is transient and that within a few days of the operation the initial vasodilatation returns to its preoperative level.[23, 36] Indeed, some workers have demonstrated a reduced blood flow in the sympathectomized paw compared to the normally innervated paw after the first few postoperative days.[11] The explanation for such findings can be shown to depend upon the state of the circulation through the normally innervated paw which is used as a control.

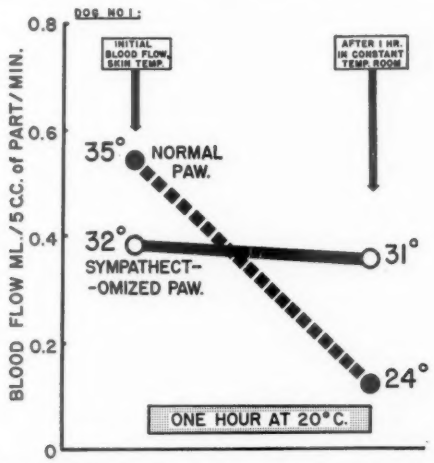

Fig. 4.—Diagram showing that circulation of normally innervated paw may be greater than denervated paw under conditions inhibiting vasoconstrictor control. This is reversed as the ambient temperature induces reflex vasoconstrictor activity.

Cannon[5] has stated that the subsidence of the initial maximal vasodilatation following sympathectomy is due at least in part to the development of increased intrinsic tone in the wall of the denervated blood vessel. For this reason agents which inhibit vasoconstrictor neural activity produce essentially maximal vasodilatation in the normally innervated paw but not in the chronically denervated paw because the blood vessels of the latter have acquired intrinsic tone not present in the intact blood vessels. This phenomenon has been demonstrated by Imig and associates[23] with hexamethonium and with anesthesia. In a similar way equivocal results may be found in the unanesthetized dog if studies are made under conditions which fail to excite vasoconstrictor activity, as shown in Fig. 4. It was noted during the preliminary observations in this study that the skin temperature of the dog in the laboratory was as high as 35° C., due to its coat of fur. At this temperature the blood flow in the paws was correspondingly great, and even without anesthesia it could not be expected that sympathectomy would produce much further demonstrable vasodilatation. It was

only when vasoconstriction was induced in the normal paw by exposing the dog to the cool ambient temperature of the constant temperature room for one hour, with the additional precaution of clipping the dog's hair to permit cooling of the skin, that the absence of vasoconstrictor activity in the chronically denervated paw could be demonstrated. By this means, it was possible to demonstrate that for at least 34 weeks some of the dogs showed no return of vasomotor control in the completely denervated paws (Fig. 1).

Just as in man, the tendency for relapse following sympathectomy of the forelimb shown in this experiment is greater than that following hindlimb sympathectomy, for in the course of another experiment in this laboratory (Petkovic, Husni, and Simeone)[35] 10 dogs have shown no return of vasomotor control up to 9 months following lumbar sympathectomy.

The results of the studies of the partially denervated forepaws provide data which do bear upon the question of vasomotor control after sympathectomy. Of first importance is the fact that the immediate result of partial denervation was often indistinguishable from that following complete denervation. This could not be regarded as a nonspecific postoperative or postanesthesia phenomenon, for no postoperative circulatory change was ever found in the control paws. However, notwithstanding the initial complete loss of vasoconstrictor tone, rapid recovery took place in 3 weeks or less. The explanation for this rapid recovery of full vasomotor control is of particular interest. It would seem to be too early for regenerative processes to be completed, even though "sprouting"[10, 33] from intact residual sympathetic fibers can be seen within 5 days of partial denervation, as shown recently by Murray and Thompson.[34]

Hypersensitivity of the denervated vessels does develop rapidly in the first few postoperative days,[13, 40] but it cannot account for the quick return of vasoconstrictor activity in this situation for the following reasons: hypersensitivity of denervated vessels can be demonstrated when there is no return of vasoconstrictor activity[40]; in these animals vasoconstrictor nervous activity was demonstrated; and hypersensitivity of effectors is in fact lost when neural control returns.[38]

A possible explanation for the rapid recovery of full vasomotor control following incomplete denervation is provided by the experiments of Simeone, Cannon, and Rosenblueth,[39] who showed that ganglia partially denervated become "sensitized" so that neurones inactivated by the partial denervation are able to respond to previously subliminal stimuli. This possibility is supported by Eccles's[9] observations that ganglion cells are excited by more than one group of preganglionic fibers, so that if some of the fibers are disconnected, sensitization of the ganglion by this partial denervation may enable the residual fibers, previously subliminal, to restore full activity of the postganglionic neurones. Reinnervation of disconnected cells by "sprouting" of the residual fibers is an additional mechanism,[10, 33, 34] but this would probably require a longer time interval. This concept of sensitization by incomplete denervation may account for Geoghegan and Aidar's theory[15] of "reorganization" following sympathectomy, where they found that nerve stimulation evoked sympathetic responses

which could not be demonstrated prior to sympathectomy. Langley[30] in 1900 had already reported that when some preganglionic fibers are severed the remainder seemed to establish functional connection with decentralized ganglion cells with which they normally had no connection. The explanation, however, may have been that connections functionally inactive before sympathectomy became active when sensitization of the ganglia was induced by partial denervation.

The observation that incomplete denervation may produce vasodilatation as great as complete denervation is especially important, because the early return of vasomotor control after what had been taken to be complete denervations has led to many different explanations for clinical relapse. In considering any theory for relapse following sympathectomy it is essential to account for permanently successful results—Goetz[17] has reported loss of vasomotor control for as long as 30 years following spmpathectomy—and for the fact that relapse is almost invariably associated with demonstrable return of neural vasoconstrictor activity.[12, 40, 41] These 2 facts discount the importance of phenomena such as the development of intrinsic vascular tone or hypersensitivity of the denervated vessels as explanations for clinical relapse.

The experiments reported here suggest that the return of vasomotor control following incomplete sympathetic denervation is early. Therefore, the relapse that occurs after several months cannot be ascribed to incomplete denervation alone. Two of these dogs showed clear evidence for the occasional functional importance of innervation from the contralateral side. Similar evidence has been described in man by Lindstrom.[32] There was no evidence for the functional importance of accessory ganglia within the nerve roots in this experiment, and although there is ample anatomic evidence for their presence[1, 27] their functional contribution to vasomotor control has never been demonstrated experimentally by means of physiologic studies.

With evidence that incomplete denervation will be followed by early return of vasomotor control, some form of regeneration must be postulated to account for late relapse after several months, such as occurred in one dog in this study (Fig. 3). Regeneration has been amply demonstrated in experimental animals,[3, 19, 30, 31] but its importance has been questioned in man.[24] There seems no room for doubt that regeneration of preganglionic fibers is possible, but to be functionally effective they must establish connection with intact postganglionic neurones. It is hard to conceive that preganglionic fibers, which are cholinergic, can grow into an extremity and behave as postganglionic neurones which are adrenergic. Experiments to achieve functional anastomosis of pre- and postganglionic axones have been unsuccessful.[22, 30] This supports the opinions of Goetz,[17] Kirgis and associates[26] and others[21, 27] that ganglionectomy is the procedure most certain to ensure complete lasting sympathetic denervation.

SUMMARY

1. It has been shown that if measures are taken to induce vasoconstriction in the normally innervated extremity used as a control it is possible to

demonstrate lasting release of vasoconstrictor neural activity following sympathectomy in dogs.

2. Vasodilatation following incomplete sympathetic denervation is at first indistinguishable from that following complete sympathectomy.

3. Incomplete denervation in the dog is characterized by recovery of vasomotor control in 3 weeks or less.

4. The mechanism of this return of vasomotor control is considered, together with a discussion of the place of incomplete denervation in the explanation of clinical relapse following sympathectomy.

REFERENCES

1. Alexander, W. F., Kuntz, A., Henderson, W. P., and Erlich, E.: Sympathetic Ganglion Cells in Ventral Nerve Roots, Science **109**: 484, 1949.
2. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities; an Experimental Analysis in Monkeys, Brit. J. Surg. **24**: 787, 1937.
3. Bacq, Z. M., and Dworkin, S.: Regeneration of Fibers of the Sympatho-adrenal System, Am. J. Physiol. **93**: 2, 1930.
4. Barcroft, H., and Hamilton, G. T. C.: Further Observations of the Results of Sympathectomy of the Upper Limbs, Lancet **255**: 770, 1948.
5. Cannon, W. B.: Factors Affecting Vascular Tone, Am. Heart J. **14**: 383, 1937.
6. Cannon, W. B.: A Law of Denervation, Am. J. Med. Sc. **6**: 737, 1939.
7. Cox, J. W., Coldwater, K. B., Randall, W. C., and Alexander, W. F.: Functional Identification of Sympathetic Pathways Through Upper Thoracic and Lower Cervical Sympathetic Trunk in Man, Fed. Proc. **13**: 31, 1954.
8. DeBakey, M., Burch, G. E., Ray, T., and Ochsner, A.: The "Borrowing-Lending" Hemodynamic Phenomenon (Hemometakinesia) and Its Therapeutic Application in Peripheral Vascular Disturbances, Ann. Surg. **126**: 850, 1947.
9. Eccles, J. C.: The Action Potential of the Superior Cervical Ganglion, J. Physiol. **85**: 179, 1935.
10. Edds, M. V., Jr.: Collateral Nerve Regeneration, Quart. Rev. Biol. **28**: 260, 1953.
11. Ederstrom, H. E., Rhode, R., and Vergeer, T.: Quantitative Changes in Blood Flow Following Experimental Denervation of the Hind Legs, Am. J. Physiol. **179**: 633, 1954.
12. Felder, D. A., Simeone, F. A., Linton, R. R., and Welch, C. E.: Evaluation of Sympathetic Neurectomy in Raynaud's Disease, SURGERY **26**: 1014, 1949.
13. Freeman, N. E., Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting From Insulin Hypoglycemia, Am. J. Physiol. **107**: 529, 1934.
14. Gask, G. E., and Ross, J. P. The Surgery of the Sympathetic Nervous System, 2nd Ed., Baltimore, 1937, William Wood and Company.
15. Geoghegan, W. A., and Aidar, O. J.: Functional Reorganization Following Pre-ganglionectomy, Proc. Soc. Exper. Biol. & Med. **50**: 365, 1942.
16. Geoghegan, W. A., Wolfe, G. A., Jr., Aidar, O. J., Hare, K., and Hinsey, J. C.: The Spinal Origin of the Pre-ganglionic Fibers to the Limbs in the Cat and Monkey, Am. J. Physiol. **135**: 324, 1942.
17. Goetz, R. H.: The Diagnosis and Treatment of Vascular Diseases, Brit. J. Surg. **27**: 146, 1949.
18. Grimson, K. S.: Sympathectomy and the Circulation—Anatomic and Physiologic Considerations and Early and Late Limitations, SURGERY **19**: 277, 1946.
19. Haimovici, H., and Hodes, R.: Pre-ganglionic Nerve Regeneration in Completely Sympathectomized Cats, Am. J. Physiol. **128**: 463, 1940.
20. Haxton, H. A.: Regeneration After Sympathectomy and Its Effects on Raynaud's Disease, Brit. J. Surg. **35**: 69, 1942.
21. Hinsey, J. C., Phillips, R. A., and Hare, K.: Observations on Cats Following Pre- and Postganglionic Sympathectomies, Am. J. Physiol. **126**: 534, 1939.
22. Hollinshead, W. H.: An Attempt to Innervate Sweat Glands Through Pre-ganglionic Fibers, J. Comp. Neurol. **89**: 193, 1948.
23. Imig, C. J., Roberson, W. J., and Hines, H. M.: Comparison of Blood Flow in Normally Innervated and in Sympathectomized Legs of Dogs After Exposure to Cold, Am. J. Physiol. **186**: 35, 1956.

24. Kinmonth, J. B., and Hadfield, G. J.: Sympathectomy for Raynaud's Disease. Results of Ganglionectomy and Pre-ganglionic Section Compared, Brit. M. J. **1**: 1377, 1952.
25. Kirgis, H. D., and Ohler, E. A.: Regeneration of Pre- and Postganglionic Fibers Following Sympathectomy of the Upper Extremity, Ann. Surg. **119**: 201, 1944.
26. Kirgis, H. D., Reed, A. F., and Pearce, G. G.: The Relative Effectiveness of Sympathetic Ganglionectomy and Section of Preganglionic Fibers in Inactivation of Smooth Muscle, SURGERY **28**: 941, 1950.
27. Kuntz, A.: The Autonomic Nervous System, 4th ed., Philadelphia, 1953, Lea & Febiger.
28. Kuntz, A., Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremity, Ann. Surg. **107**: 25, 1938.
29. Langley, J. N.: Note on the Connection With Nerve Cells of the Vasomotor Nerves for the Feet, J. Physiol. **12**: 347, 1891.
30. Langley, J. N.: Notes on the Regeneration of the Pre-ganglionic Fibers in the Sympathetic System, J. Physiol. **25**: 417, 1900.
31. Lee, F. C.: The Regeneration of Sympathetic Nerve Fibers, Research Publ., A., Nerv. & Ment. Dis. **9**: 417, 1930.
32. Lindstrom, B. L.: Communicating Branches Between Lumbar Sympathetic Chains, Acta chir. scandinav. **109**: 432, 1955.
33. Morris, D. D. B.: Recovery in Partly Paralyzed Muscles, J. Bone & Joint Surg. **35**: 650, 1953.
34. Murray, J. G., and Thompson, J. W.: The Occurrence and Function of Collateral Sprouting in the Sympathetic Nervous System of the Cat, J. Physiol. **135**: 133, 1957.
35. Petkovic, D. S., Husni, E. A., and Simeone, F. A.: Sympathetic Control of the Circulation in the Hind Limb of the Dog, Am. J. Physiol. In press.
36. Randall, W. C., Alexander, W. F., Hertzman, A. B., Cox, J. W., and Henderson, W. P.: Functional Significance of Residual Sympathetic Pathways Following Verified Lumbar Sympathectomy, Am. J. Physiol. **160**: 441, 1950.
37. Sheehan, D., and Marrazzi, A. S.: The Sympathetic Pre-ganglionic Outflow to the Limbs of Monkeys, J. Neurophysiol. **4**: 68, 1941.
38. Simeone, F. A.: The Effect of Regeneration of the Nerve Supply on the Sensitivity of the Denervated Nictitating Membrane to Adrenine, Am. J. Physiol. **120**: 466, 1937.
39. Simeone, F. A., Cannon, W. B., and Rosenblueth, A.: Sensitization of Superior Cervical Ganglion to Nerve Impulses by Partial Denervation, Am. J. Physiol. **122**: 94, 1938.
40. Simeone, F. A., and Felder, D. A.: The Supersensitivity of Denervated Digital Blood Vessels in Man, SURGERY **30**: 218, 1951.
41. Simmons, H. T., and Sheehan, D.: The Causes of Relapse Following Sympathectomy of the Arm, Brit. J. Surg. **27**: 234, 1939.
42. White, J. C., Smithwick, R. H., and Simeone, F. A.: The Autonomic Nervous System, 3rd ed., New York, 1952, The Macmillan Company.

DISCUSSION

DR. F. A. SIMEONE.—I would like to emphasize one or two thoughts. The data presented will have far-reaching basic significance beyond explaining some of the recurrences after sympathectomy for peripheral vascular disease. I refer here to the anatomy of the sympathetic outflow from the central nervous system. Most of our concepts on this are based upon the charting of surface effects of ablations and stimulations of sympathetic rami or of the sympathetic trunk itself at various levels. The data that Dr. Tracy has just presented point out that the demonstration of sympathetic paralysis, based upon tests performed immediately or shortly after severance of certain preganglionic rami, does not necessarily mean that the postganglionic cells in question have lost all their preganglionic connections with the central nervous system. Similarly, when isolated preganglionic rami are stimulated, the failure to obtain surface or other effects cannot imply that those rami which are being stimulated do not have connections with postganglionic cell bodies innervating the areas being observed. From the information we have described, it is obvious that following sympathectomy there may be residual preganglionic connections with postganglionic neurones which are subliminal for excitation of the respective postganglionic neurones until some time has elapsed. The sensitivity of the ganglionic cells may then change to the extent that stimulation of the same residual preganglionic fibers does attain threshold and the appropriate effects of stimulation are detectable. This phenomenon does not imply regrowth or reorganization of nerve fibers and their connections but, merely, an altered sensitivity of postganglionic neurones.

RECOGNITION AND TREATMENT OF RENAL ARTERIAL STENOSIS ASSOCIATED WITH HYPERTENSION

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STENOSIS of a renal artery is now recognized as one cause of severe, symptomatic, progressive, arterial hypertension, which may be relieved if unobstructed blood flow to the kidney is restored. Nephrectomy may be necessary if the conservative operation is technically impossible or if the kidney has been severely damaged beyond the obstructed vessel.

Seven patients with hypertension and renal arterial narrowing treated surgically at Ochsner Foundation Hospital form the basis of this report. In 2 patients a conservative surgical procedure resulted in relief of all symptoms and restoration of normotension for 18 and 6 months, respectively; in 3 nephrectomy was performed, and in 2 the renal arterial stenosis was incidental and insignificant.

The initial interest in the relationship between renal disease and hypertension was directed toward primary renal parenchymal disease with actual or presumed secondary renal ischemia. The first successful attempt at reversal of hypertension followed nephrectomy for unilateral atrophic pyelonephritis.[10] This subject was ably reviewed by Smith.[54] The experimental investigations of Goldblatt and others [21, 22] indicated that under certain circumstances arterial hypertension could be induced in animals by renal arterial stricture.

Only in recent years has it become increasingly apparent that hypertension in man may be due to stenosis of a renal artery. The evidence consists of a large number of reported cases in which the clinical picture of developing severe hypertension can be well correlated with post-mortem observations[36, 41, 57] and with a series of cases of hypertension associated with stenosis of a renal artery in which the blood pressure returned to normal and remained normal for more than a year after removal of the affected kidney.[36, 41] Recently, a few similar cases have been reported in which the hypertension was corrected by restoration of unobstructed blood flow.[19, 43]

The physiologic basis for development of hypertension secondary to stenosis of a renal artery is similar to that of hypertension secondary to coarctation of the aorta proximal to the renal arteries. After considerable debate the experimental observations of Scott and co-workers[11, 51, 52] and others[25, 26, 48] indicate that a renal humoral mechanism is at least in part responsible for the hypertension of coarctation of the aorta. Some of the critical observations are: if thoracic coarctation is produced in a dog, hypertension will result; if one kidney

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is removed and the other is transplanted to the neck proximal to the coarctation, the hypertension disappears; and if one kidney is removed and the other is transplanted to the thigh, remaining distal to the coarctation, the hypertension persists. That renal function and renal blood flow are normal in coarctation of the aorta suggests a renal humoral mechanism that produces systemic hypertension so early and so effectively that no measurable reduction in renal blood flow (ischemia) develops.

Hypertension due to unilateral renal arterial stenosis differs from that due to coarctation of the aorta in that the contralateral kidney is exposed to the full effects of the hypertension. Data are limited, but clinical observations under these circumstances suggest that the blood flow through the 2 kidneys may, as ordinarily measured, be equal. The renal function is presumably normal and equal on both sides except in the presence of severe degrees of arterial stenosis. Atrophic changes then occur. Usually, as in coarctation of the aorta, systemic hypertension drives sufficient blood past the stenosis to permit adequate renal nourishment and function on the involved side. Apparently on the other side, to prevent excessive blood flow as the result of the hypertension and the open vascular tree, intrarenal arteriolar spasm serves to maintain the renal blood flow at a normal level.

In cases of unilateral renal arterial stenosis and hypertension the kidney on the side of the stenosis is completely protected from the hypertension so that vascular changes within that kidney are either absent or develop from other disease. The contralateral kidney is exposed to the hypertension, which may be extremely severe and progress to necrotizing arteriolitis.[5, 33] With removal of the stenotic lesion or the kidney on that side, considerable function of the other kidney may be restored.[40] Unless renal ischemia on the involved side is extreme with secondary fibrosis and atrophy, the kidney on the side of the stenosis may be the better kidney, and it is for this reason that conservative surgical therapy is doubly attractive.

In man it is apparent that if only one kidney[3] or even a part of one kidney[6, 41] lies distal to an arterial stenotic lesion systemic hypertension may develop. In cases of renal infarction hypertension is characteristically transient[2, 12, 58] or it may be absent.[2] This suggests that some blood must leave the ischemic kidney for hypertension to ensue.[7]

PATHOLOGIC PHYSIOLOGY

Any lesion that gives rise to a significant degree of renal arterial stenosis may precipitate hypertension. Omitted from this discussion are cases of primary renal disease in which secondary renal ischemia may develop. Although the total number of reported cases of hypertension due to stenosis of a renal artery is small, a surprising variety of lesions may precipitate this complication, as is indicated by the following etiologic classification of proved or strongly presumptive reported cases of hypertension secondary to stenosis of one or both renal arteries.

A. Congenital
   1. Stenosis confined to the renal artery[9, 23, 24, 28, 34, 43] (Cases 2 and 3)

2. Abdominal aortic coarctation with associated renal arterial stricture[18]
3. Renal arterial aneurysm (in older patients some undoubtedly acquired)[29, 53, 55] (Case 1)
4. Aortic anomaly occluding renal artery[1]
5. Multiple renal arteries with stenosis or occlusion of one or more[28, 41] (Case 1)

B. Acquired

1. Atherosclerosis
   a. Sclerosis of renal artery[49, 50] (Case 5)
   b. Sclerotic plaque in aorta occluding renal artery[15, 19, 37, 42, 45, 56, 59] (Case 4)
   c. Ascending thrombotic occlusion of aorta[20, 30, 46, 47]
   d. Abdominal aortic aneurysm occluding renal artery[27]
   e. Acquired renal arterial aneurysm[39, 57]
2. Thromboangiitis of renal artery[35]
3. Idiopathic thrombosis of renal artery[33]
4. Emboli to a renal artery
   a. Simple embolus[17]
   b. Mycotic embolus[8]
5. Syphilitic arteritis[44]
6. Trauma
   a. Traumatic thrombosis[38]
   b. Traumatic hematoma[16]
   c. Traumatic arteriovenous fistula[4]
   d. Foreign body occlusion[33]
7. Extrinsic tumor[28, 50]
8. Extrinsic fibrous bands[31]
9. Hydatid cyst compressing renal artery[13]

A survey of the medical literature indicates that renal arterial stenosis associated with atherosclerosis is the commonest type of lesion, and this is probably true. However, in the past, clinical suspicion of renal arterial stricture was slight, and frequently operative and even necropsy reports have indicated that essential observations were omitted. Careful clinical, operative, and post-mortem observations will have to become more general before any accurate idea is obtained regarding the total and relative incidence of various types of renal arterial stenosis.

In our limited experience we have been impressed with the occurrence of this lesion in children. At this early age, when essential hypertension is extremely uncommon, renal arterial stenosis, presumably congenital, assumes major significance. In the middle decades of life, when essential hypertension is common, search for cases due to renal arterial stenosis is tedious and difficult. After the age of 50 years, when the onset of essential hypertension is uncommon, the appearance of persistent diastolic hypertension demands careful study of the aorta and renal arteries regardless of the demonstration of normal renal function and a normal excretory urogram.

CLINICAL MANIFESTATIONS

The symptoms and signs of this variety of hypertension are unfortunately not unique. The hypertension is generally severe with a fixed high diastolic

pressure and rapid progression of all symptoms and signs. Headache, malaise, and visual disturbances develop, and both heart failure and renal failure may supervene. Transition to malignant hypertension is often rapid. Pain is uncommon unless an acute infarction develops. We have not been impressed with the appearance of polyuria or leukocytosis, as have others.[36] Polydipsia and polyuria occurred in Case 1 to be presented later.

Signs of cardiac or renal failure depend upon the stage of the disease. Roentgenographic evidence of cardiac enlargement and electrocardiographic evidence of left ventricular hypertrophy with anterolateral ischemia are common. With acute infarction of the kidney, pain and tenderness in the loin are often present. Characteristically, renal function as usually measured remains normal until an advanced stage of the disease. No abnormalities are demonstrated in excretory urograms unless renal infarction or complete loss of renal function has occurred. Even here in the retrograde pyelogram the pattern is normal although the kidney may be somewhat small.

DIAGNOSIS

The diagnosis of this lesion is difficult to make. As already indicated, the extremes of age plus certain clinical characteristics may arouse suspicion. Results of urinalysis, the usual renal function studies and intraveonus and retrograde pyelography are usually normal.

Definite diagnostic information may be obtained by renal arteriography. The indications for arteriography in patients with hypertension have not yet been crystallized. At present we perform it, in the absence of primary renal disease, on all patients whose hypertension developed before the age of 25 years and on all in whom persistent severe diastolic hypertension develops after the age of 50 years. On other patients in the usual age group of patients with essential hypertension, we perform aortography if there is something in the history of their disease that does not conform with the usual natural history of essential hypertension. We have as yet had little experience, but additional valuable information may be obtained by unilateral application of clearance methods, particularly the renal plasma clearance. The differential determination of urinary sodium and potassium has been capricious.

With suitable precautions we have found arteriographic study most helpful. In adults this is done by the translumbar approach with the aid of a local anesthetic. Scout films and pyelograms indicate the location of the kidneys and suggest the proper level for injection of dye. If the needle is placed too low, the renal arteries will not be visualized. If it is placed too high, a considerable quantity of the dye will be dissipated in the vessels of the celiac axis and superior mesenteric artery, and visualization of the renal artery will be poor. We inject rapidly 20 ml. of a 50 per cent solution of Hypaque through a large bore 18 French needle. A roentgenographic picture is taken as the injection is being concluded. Two or more injections may be required to outline both renal arteries accurately. In a child dye is injected in a retrograde direction by passage of a catheter up from the femoral artery. We have had some difficulty in interpreting cases with borderline degrees of stenosis. This must be checked at operation

by accurate measurement of the pressures proximal and distal to the stenosis. If the pressure across the stricture does not drop significantly, the stenosis is not a significant etiologic factor in the hypertension. A significant fall in pressure is strong presumptive evidence that the stenosis is responsible for the hypertension.

CASE REPORTS

CASE 1.*—W. R. L., a white male infant 9 months old, was admitted to Ochsner Foundation Hospital July 28, 1952, because of vomiting and failure to gain weight for the preceding 3 months. Polydipsia, polyuria, albuminuria, and hyposthenuria were present and the blood pressures ranged from 200 to 260 mm. Hg systolic and 160 to 190 mm. Hg diastolic. Renal function, excretion of dye by the kidneys, and intravenous and retrograde pyelograms were repeatedly normal. A series of strictures and aneurysmal dilatation of reduplicated right renal arteries was noted in the arteriogram. Right nephrectomy was performed on Sept. 26, 1952, by Dr. Edgar Burns with confirmation of the arteriographic findings (Fig. 1) and prompt relief of the hypertension and all symptoms and signs. Four years and eight months later, this boy is in perfect health, results of urinalyses have been repeatedly normal, and his blood pressure has been 90 mm. Hg systolic and 70 mm. Hg diastolic since shortly after the operation.

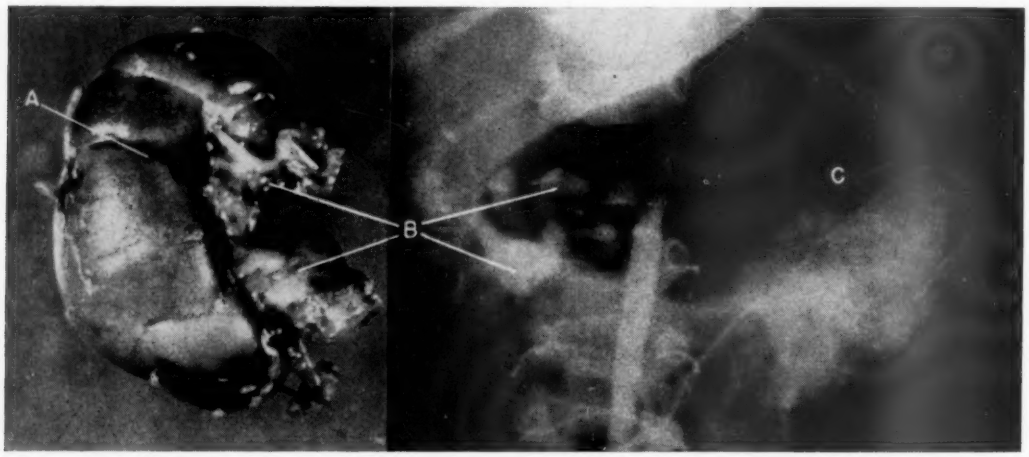


Fig. 1.—Case 1. W. R. L. Arteriogram and resected right kidney demonstrating a series of strictures and aneurysms of reduplicated right renal artery.

This is a case of congenital aneurysm and stricture with extreme hypertension in an infant cured by nephrectomy.

CASE 2.†—J. L. C., a white girl 10 years old, was admitted to Ochsner Foundation Hospital Nov. 20, 1955, because of headaches, malaise, epistaxis, and hypertension (ranging from 170 to 280 mm. Hg systolic and 120 to 170 mm. Hg diastolic) of 5 months' duration.

Pyelograms and abdominal exploration elsewhere demonstrated absence of the right kidney. Tests elsewhere and on admission ruled out an endocrine tumor. A normal left kidney was visualized in the intravenous (Fig. 2) and retrograde pyelograms. Renal function was normal. In the renal arteriogram an elongated stricture of the left renal artery at its origin with poststenotic dilatation was demonstrated (Fig. 3, *A* and *B*).

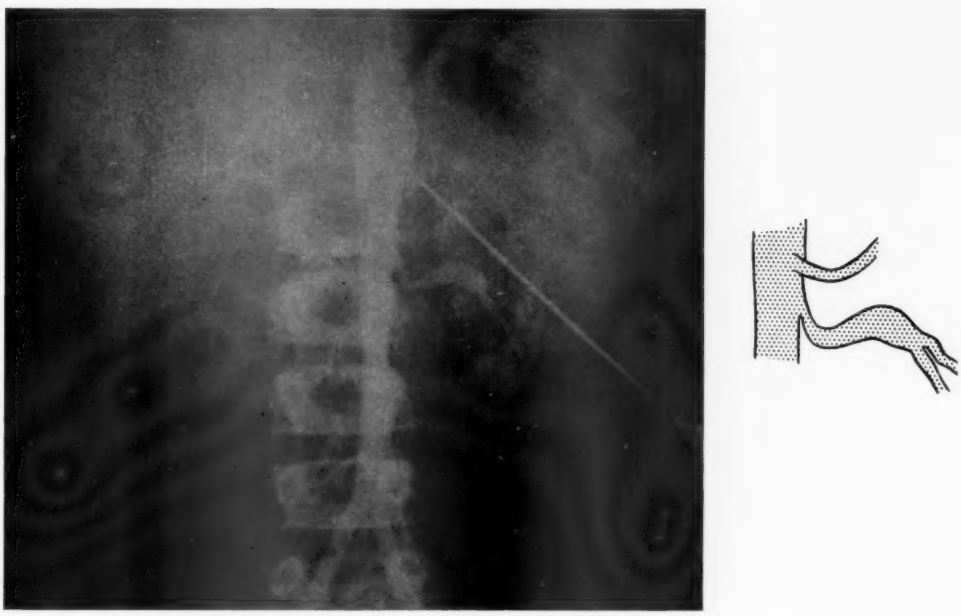
Observations at operation on November 28 were the same as had been indicated by arteriography. There was a thrill in the left renal artery and the tension was palpably low distal to the stricture. The spleen was removed. The splenic artery was divided in its midportion and end-to-side splenorenal arterial anastomosis was performed with interrupted

*This case was previously reported in detail by Snyder and associates[55] and will be presented only briefly here.

†This case has been presented in detail elsewhere.[14]

simple sutures of 5-0 arterial silk. The renal artery was occluded for 15 minutes. The postoperative course was uneventful and renal function was good. After the sixth postoperative day the blood pressure never rose above 130 mm. Hg systolic and 80 mm. Hg diastolic. All symptoms were relieved and the patient has remained normotensive and has shown a remarkable gain in height and weight in the 18 months since operation.

Fig. 2.—Case 2. J. L. C. Intravenous pyelogram demonstrating the normal configuration and function of the solitary left kidney.



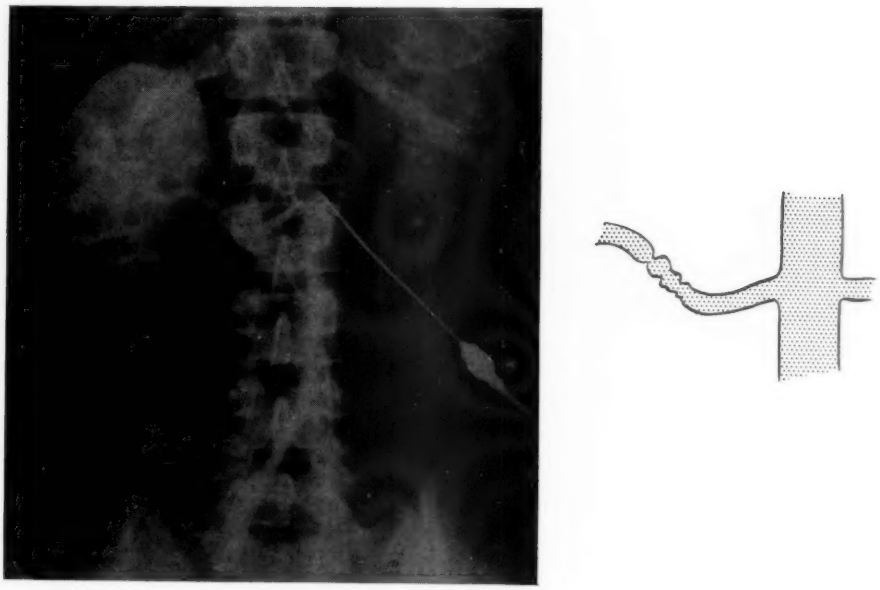
A. *B.*

Fig. 3.—Case 2. J. L. C. *A*, Renal arteriogram demonstrating severe juxta-aortic stenosis of the left renal artery with poststenotic dilatation. *B*, Diagrammatic representation of same.

CASE 3.—W. A. H., a white man 23 years old, was admitted to Ochsner Foundation Hospital on Nov. 28, 1956, because of severe hypertension and headaches associated with nausea and vomiting of one year's duration.

He had been in another hospital for 5 months without improvement. Tests elsewhere and on admission indicated that the lesion was not an adrenal tumor. The blood pressure was 230 mm. Hg systolic and 150 mm. Hg diastolic. Results of routine laboratory studies were normal except for electrocardiographic demonstration of left ventricular hypertrophy with anterolateral ischemia. No abnormalities were detected in the intravenous pyelogram

Fig. 4.—Case 3. W. A. H. Intravenous pyelogram demonstrating the normal configuration and function of the 2 kidneys.



A. *B.*

Fig. 5.—Case 3. W. A. H. *A*, Renal arteriogram demonstrating a series of strictures in the right renal artery. A second arteriogram demonstrated a normal artery on the left. *B*, Diagrammatic representation of same.

(Fig. 4) or on retrograde pyelography. Normal vessels on the left side were seen in a renal arteriogram. On the right side the vessel was long, and there was a series of strictures extending from 1.5 to 3.5 cm. from the origin of the vessel (Fig. 5, *A* and *B*). These observations were confirmed at operation on Dec. 18, 1956. Pressure proximal to the strictures was 180/160 mm. Hg whereas distal to the block there were no pulsations and a mean systolic pressure of 25 mm. Hg was recorded (Fig. 6). The constricted segment was excised and

end-to-end anastomosis was performed with simple end-on sutures of 5-0 arterial silk (Fig. 7). The renal artery was occluded for 40 minutes. Sections of the strictured artery revealed extensive fibromuscular proliferation of the media with no changes of note in the intima (Fig. 8, *A* and *B*).

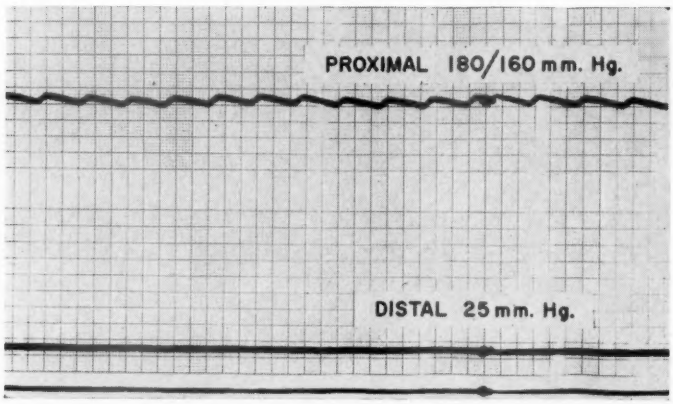


Fig. 6.—Case 3. W. A. H. Operative right renal arterial pressures proximal and distal to stenotic segment.

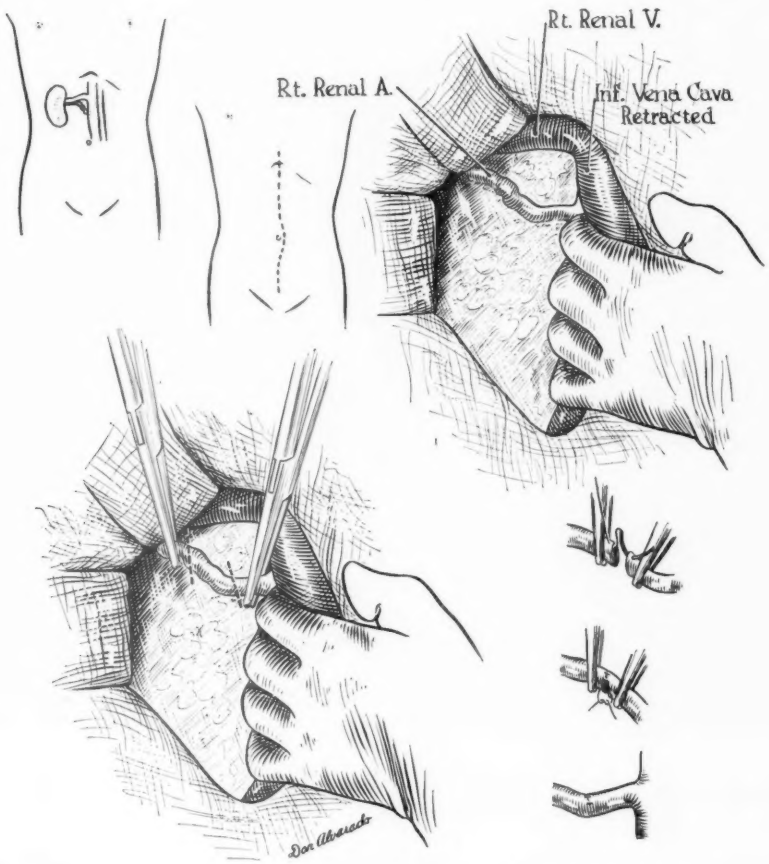
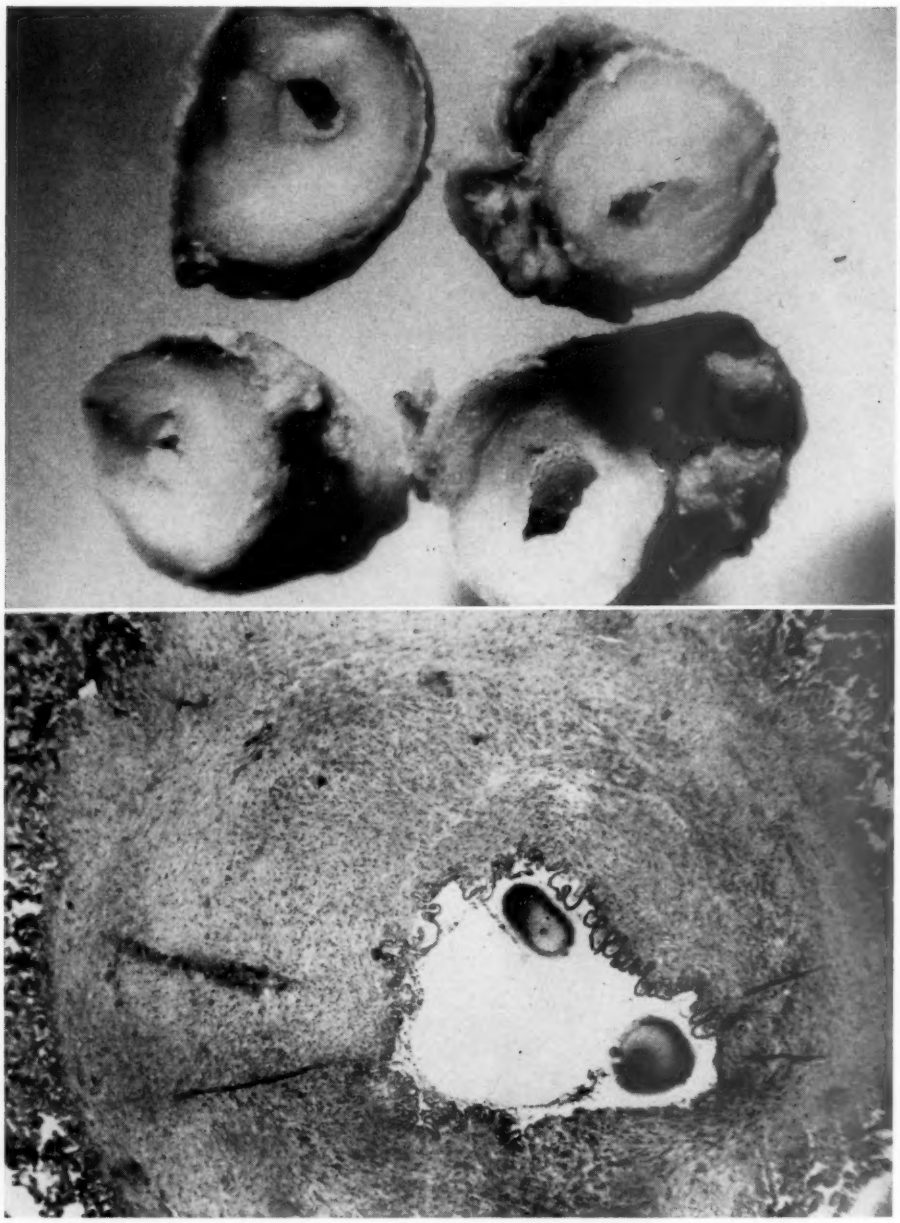


Fig. 7.—Case 3. W. A. H. Operative findings and technique. Posterior peritoneal division, dissection of the duodenum to the right, small bowel evisceration and division of the right spermatic vein permitted retraction of the inferior vena cava to the left and exposure of the right renal artery.

Postoperatively, urinary output was normal and no complications developed. At the time of discharge on December 28, the blood pressure was 150 to 160 mm. Hg systolic and 96 to 110 mm. Hg diastolic. An open vessel was demonstrated in the renal arteriogram (Fig. 9).

A.



B.

Fig. 8.—Case 3. W. A. H. *A*, Low-power magnification of transverse sections of the specimen. *B*, Microscopic section reveals a normal intima, an intact internal elastic lamina, with pronounced fibromuscular proliferation of the inner longitudinal layer of the media.

All symptoms disappeared and a normal blood pressure ensued. On examination 6 months after operation, the patient was asymptomatic and his blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic. Electrocardiographic findings were still abnormal.

Cases 2 and 3 are examples of congenital stenosis of a renal artery in which all symptoms and signs were relieved by an appropriate reconstructive arterial procedure.

CASE 4.—G. D. F., a white man 69 years old, was admitted March 8, 1956, with a chief complaint of high blood pressure for 10 years. He had been asymptomatic until the preceding 4 months when he began to experience episodic bouts of left ventricular failure and pain, requiring morphine for relief. He also had had attacks of nausea and vomiting and had lost 15 pounds during these 4 months. Vigorous antihypertensive drug therapy had been ineffectual.

Fig. 9.—Case 3. W. A. H. Postoperative renal arteriogram demonstrates an open arterial channel.

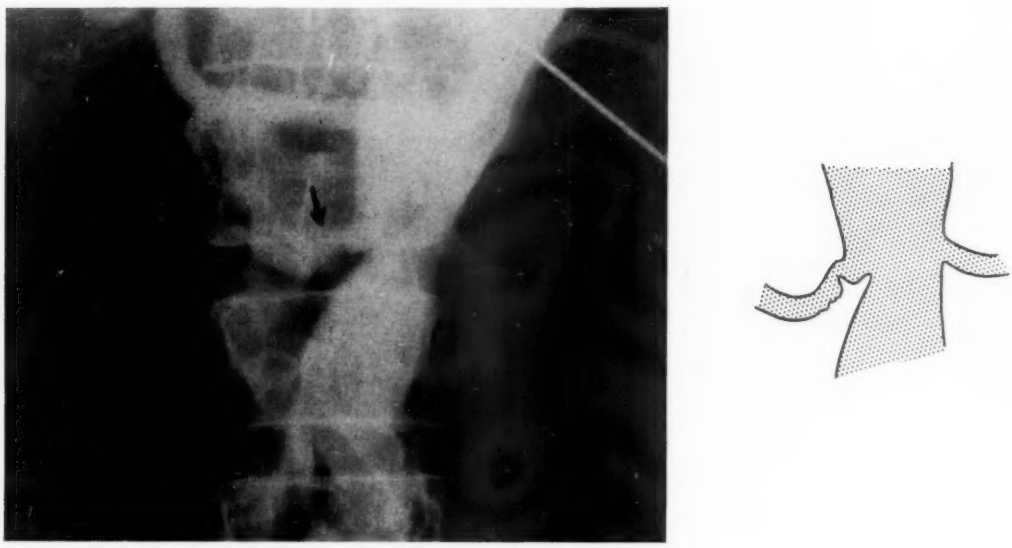
Blood pressures ranged from 218 to 264 mm. Hg systolic and from 106 to 152 mm. Hg diastolic. Antipressor drug therapy was ineffectual. Results of routine urinalysis, blood count, blood sugar, and blood urea nitrogen values were normal. Definite evidence of myocardial disease and left ventricular hypertrophy with anterolateral ischemia was noted in the electrocardiogram. Results of serologic tests for syphilis were negative. Renal function was normal. Results of intravenous and retrograde pyelography were normal. Results of tests for pheochromocytoma were negative. In the renal arteriogram (Fig. 10, *A* and *B*) narrowing of the aorta was noted at the renal level with gross narrowing of the origin of the right renal artery, which was suggestive of an occluding plaque.

It was believed that on the mild chronic arteriosclerotic hypertension had been grafted severe diastolic hypertension probably related to the stenosis of the right renal artery. In view of the repeated episodes of left ventricular failure it was deemed unwise to subject the patient to prolonged conservative surgical reconstruction and that nothing more than nephrectomy should be attempted. This was performed on March 16, 1956, by Dr. Edgar Burns. The kidney weighed 130 Gm. and contained extensive segments of cortical scarring with lymphocytic infiltration, nephron atrophy, and fibrosis and hyalinization of the glomeruli. There was no evidence of necrotizing arteriolitis. In the major renal artery extensive sclerosis and intimal fibrosis were noted.

The postoperative course was difficult and the blood urea nitrogen level rose to 37 mg./100 ml. The patient was discharged on the fourteenth postoperative day after his blood pressure had been controlled by Ecolid and Serpasil. At home, his blood pressure fell progressively and use of antihypertensive drugs was discontinued. However, severe

cerebral circulatory insufficiency developed and the patient died about 3 weeks later. At autopsy extensive arteriosclerosis was present but the remaining kidney appeared to have functioned well.

In this case the renal arterial stricture was due to an arteriosclerotic plaque in the aorta occluding the lumen of the right renal artery. There was a delayed fall in the high blood pressure with increasing evidence of cerebrovascular insufficiency. This suggests that only with high blood pressure could enough blood traverse the sclerotic vessels to the brain. At normal pressures insufficient blood reached the brain.



A. *B.*

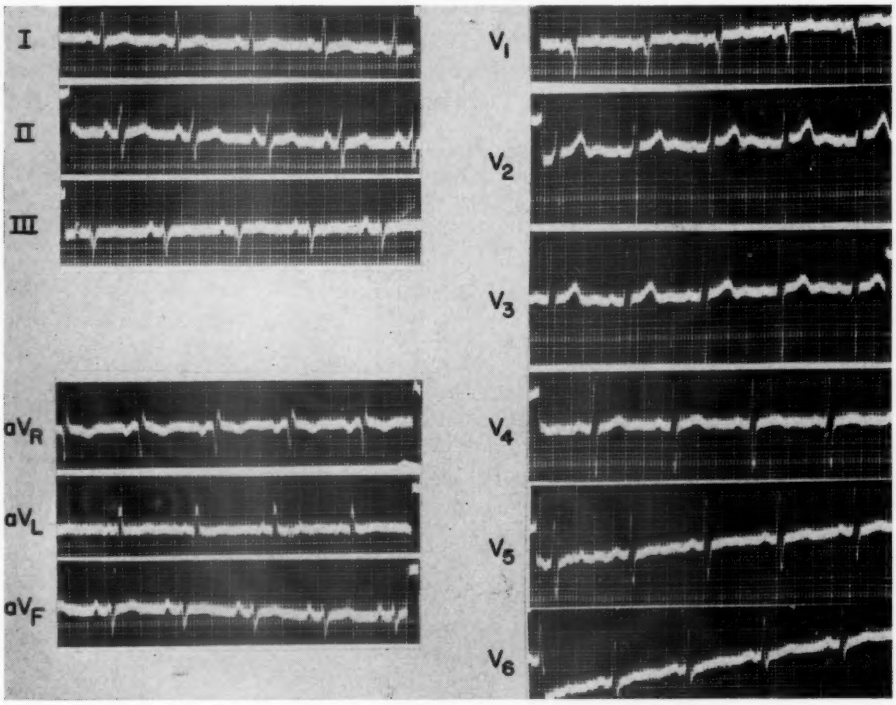
Fig. 10.—Case 4. G. D. F. *A*, Renal arteriogram demonstrates deformity of the aorta with severe stenosis of the origin of the right renal artery indicating an aortic plaque occluding the orifice of the renal artery. *B*, Diagrammatic representation of same.

CASE 5.—R. D. S., a white man 64 years old, was admitted to Ochsner Foundation Hospital on Feb. 2, 1957, complaining of hypertension and blurred vision for 4 months. Repeated blood pressure determinations at home ranged from 200 to 235 mm. Hg systolic and 110 to 160 mm. Hg diastolic. Two weeks earlier a transient attack of left facial numbness and weakness had occurred.

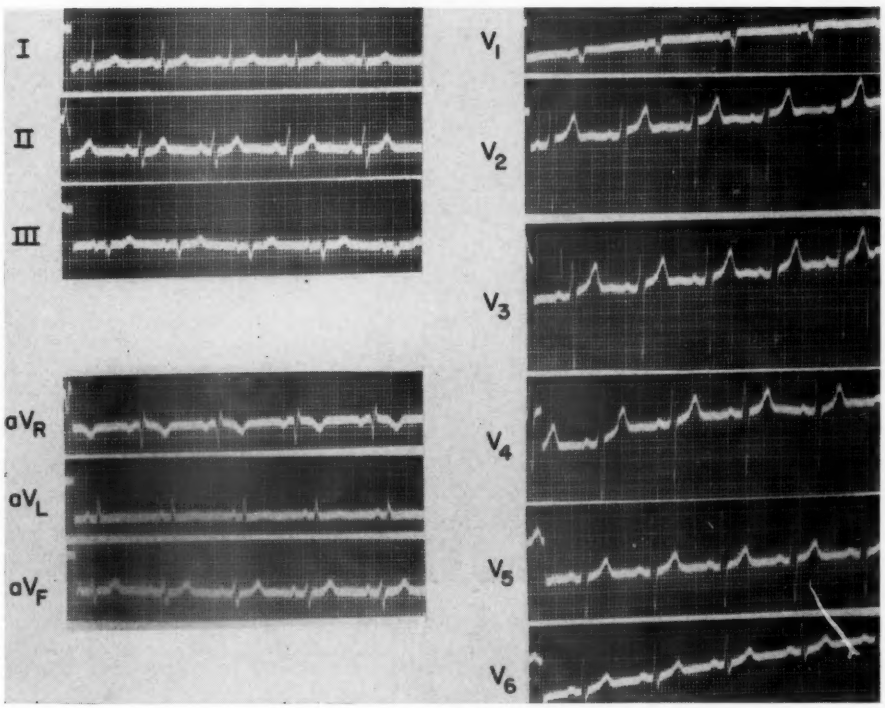
Results of routine blood studies and blood urea nitrogen values were normal. In the intravenous urogram the right kidney was seen to be smaller than the left. Excretion of dye was better in the left kidney. Evidence of left ventricular hypertrophy with anterolateral ischemia was noted in the electrocardiogram (Fig. 11, *A*). Normal vessels on the left were visualized in the renal arteriogram. On the right the vessel did not fill for the first 5 mm. of its course (Fig. 12, *A* and *B*).

At operation on Feb. 13, 1957, a sclerotic plaque was found almost completely occluding the origin of the right renal artery for a distance of 1 cm. The proximal pressure was 170/100 mm. Hg and the distal 70/60 mm. Hg. Through a longitudinal incision in the vessel and endarterectomy, the occlusive material was removed but adequate vascular continuity could not be established. This segment was resected and the vessel was implanted lower into the aorta. This maneuver was unsuccessful because the tension was too great. The report of biopsy of both kidneys was grade 2 nephrosclerosis. Right nephrectomy was performed. There was little change in blood pressure during the uncomplicated postoperative course. After discharge all symptoms disappeared and improvement in general health and activity was pronounced.

On examination 3 months after operation the blood pressure was 170 mm. Hg systolic and 110 mm. Hg diastolic. Results of routine laboratory tests were normal. Preoperative electrocardiographic abnormalities had disappeared (Fig. 11, *B*).



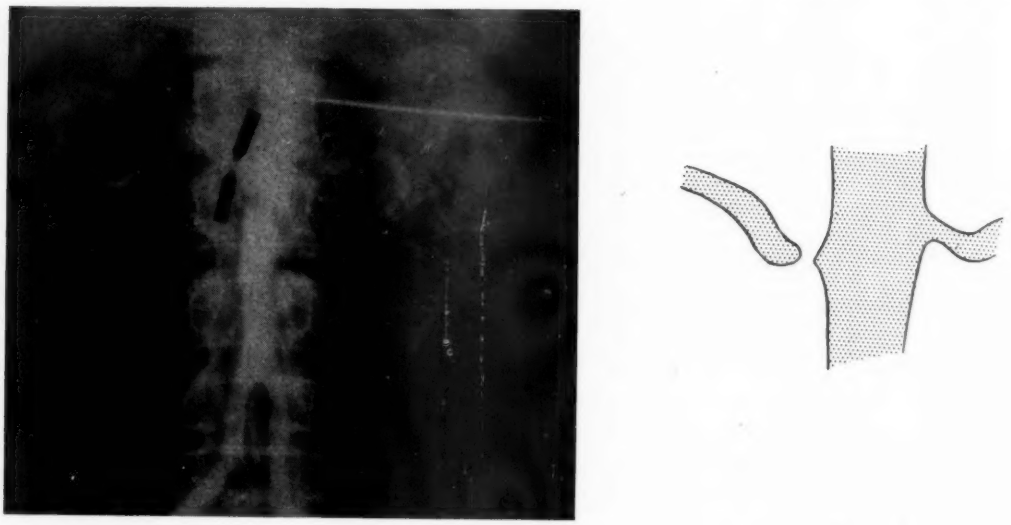
A.



B.

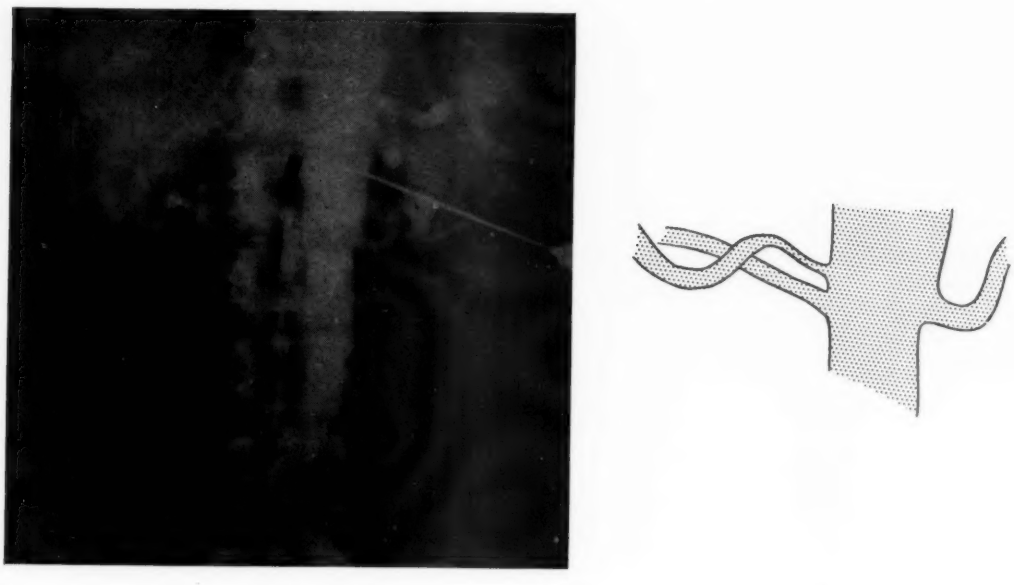
Fig. 11.—Case 5. R. D. S. *A*, In the preoperative electrocardiogram definite evidence of left ventricular hypertrophy with anterolateral ischemia is demonstrated. *B*, In the postoperative electrocardiogram these changes are absent.

In this case arterial stenosis contributed to the hypertension although undoubtedly a nephrosclerotic component was also present. Conservative surgical measures were unsuccessful. In such a small vessel a transverse incision for endarterectomy would have been preferable. If endarterectomy proved unsuccessful, the segment could have been excised and the distal



A. *B.*

Fig. 12.—Case 5. R. D. S. *A*, Renal arteriogram demonstrates almost complete absence of the lumen of the proximal centimeter of the right renal artery. *B*, Diagrammatic representation of same.



A. *B.*

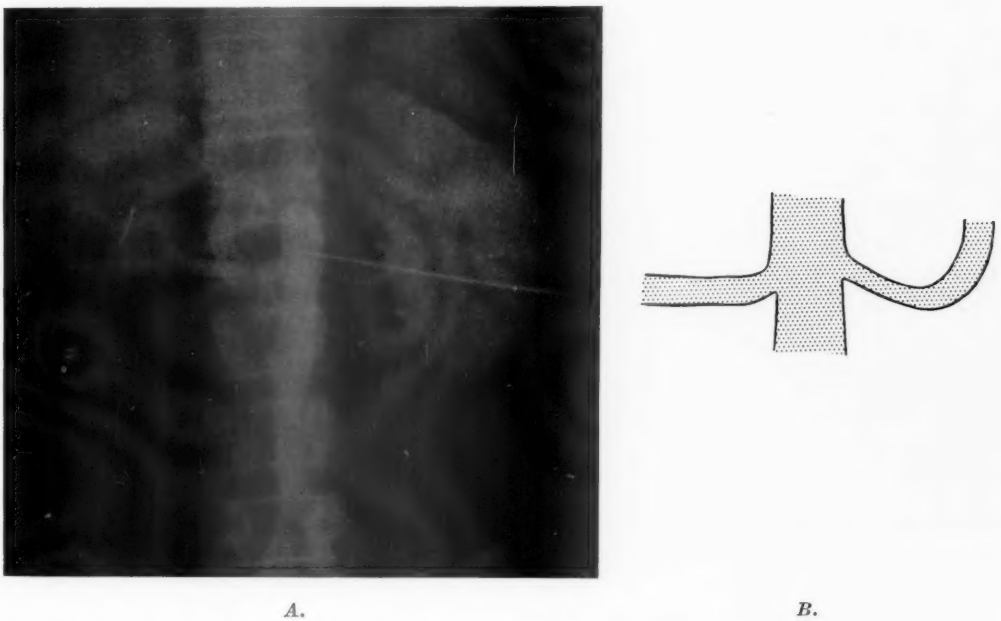
Fig. 13.—Case 6. A. L. R. *A*, Renal arteriogram demonstrates a moderate degree of stenosis of one of 2 arteries to the right kidney. *B*, Diagrammatic representation of same.

end anastomosed to the original aortic orifice. (Our anastomosis was made lower and contributed to the serious tension of the suture line.) Since surgical reconstruction was unsuccessful, nephrectomy was indicated because the function of this kidney was reduced and

the contralateral kidney had normal function. Postoperatively, pronounced clinical improvement was noted by the patient and 2 local physicians. Reduction in the blood pressure and reversal of the abnormal electrocardiographic findings suggest that the severe component of the hypertension due to the renal arterial stenosis has been relieved, and the patient now has evidence of residual, relatively benign, arteriosclerotic hypertension.

CASE 6.—A. L. R., a white man 56 years old, was admitted to Ochsner Foundation Hospital on Jan. 11, 1957, with known hypertension for more than 10 years and significant progression of the disease during the preceding year in spite of vigorous treatment. The blood pressure ranged from 260 to 300 mm. Hg systolic and from 100 to 170 mm. Hg diastolic. Results of routine studies and renal function tests were normal. Satisfactory renal excretion was demonstrated in the intravenous urogram. The result of the Regitine test was normal. A normal vessel on the left was noted in the renal arteriogram. On the right side there were 2 renal arteries (Fig. 13, *A* and *B*), the upper one being considerably stenosed.

At exploration on Jan. 18, 1957, the upper right renal artery was found to be stenosed but intra-arterial pressures proximal and distal to the stenosis were identical. The wound was closed. The patient was extremely ill for several days but recovered and was discharged on the sixteenth postoperative day. The extreme hypertension has been somewhat better controlled by more vigorous drug therapy.



A. *B.*

Fig. 14.—Case 7. P. J. St. R. *A*, Renal arteriogram demonstrates a moderate degree of stenosis of the left renal artery. *B*, Diagrammatic representation of same.

CASE 7.—P. J. St. R., a white man 44 years old, was admitted to Ochsner Foundation Hospital Jan. 17, 1957, because of known hypertension for 2 years. Recently, he had become temporarily blind because of a retinal hemorrhage. Arterial pressure was 240 mm. Hg systolic and 115 mm. Hg diastolic. Results of routine laboratory studies, renal function test, intravenous urography, and electrocardiography were all normal. Some narrowing of the left renal artery was noted in the renal arteriogram (Fig. 14, *A* and *B*).

At operation on Feb. 1, 1957, the pressures proximal and distal to the stenosis were identical. Bilateral splanchnicectomy and celiac ganglionectomy were performed. Postoperatively, the blood pressure was easily controlled with Serpasil alone.

DISCUSSION

In Cases 6 and 7 the patients proved not to have significant arterial stenosis. Patients with duplicated arterial blood supply to one kidney often have significant arterial stenosis or thrombosis.[55] In Case 6 a sharp constriction was present in one vessel but evidently enough collateral blood flow occurred through the second to maintain the distal circulation. In Case 7, in retrospect, the stenosis was mild and it should not have been considered as the cause of the hypertension.

In the restoration of circulation through vital but small renal arteries, meticulous care must be taken to ensure permanent adequate blood flow. For this reason, we prefer not to employ foreign grafts (either homografts or plastic grafts), particularly in children. It should be possible in most instances to use the patient's own vessels. The splenic artery courses only 1 or 2 cm. from the left renal artery, and, unless it is diseased, it should be readily available for lesions of the left renal artery. We prefer end-to-side anastomosis because disparity in the size of the vessels is immaterial, the normal circulation through the renal artery is preserved, and it has been amply demonstrated in operations on the small arteries of the leg that stenosis is less apt to occur after end-to-side than after end-to-end anastomosis. Removal of the spleen is probably not necessary. Although in Case 2 a left thoracic abdominal incision was used, I now prefer to approach either side through a midline abdominal incision. Dissections on cadavers suggest that the splenic artery is long enough so that it could be swung over and used to reconstruct the right renal artery. This has also been suggested by Hurwitt and co-workers.[30]

As in our Case 3, excision of the stricture and direct anastomosis of the vessel may be possible. Endarterectomy undoubtedly is sometimes indicated, and some successful cases have been reported.[19, 41] This technique is most useful in patients with sclerotic plaques of the abdominal aorta that are occluding the orifice of the renal artery. Care must be taken not to leave a distal intimal flap. In cases in which a sclerotic plaque is present primarily in the renal artery (as in Case 5) great care is necessary if endarterectomy is to be successful because the vessel is relatively small. The best technique is probably that of Julian and co-workers[32] in which the vessel is divided distally and the outer layers are peeled back as the occluding material is enucleated.

SUMMARY

Seven cases of hypertension associated with renal arterial stenosis have been presented. In 2 cases of congenital origin, excellent results followed conservative surgical arterial reconstruction. In one case of congenital aneurysms and stenosis in an infant, cure followed nephrectomy. In 2 cases, arteriosclerotic plaques produced significant hypertension; in one, elective nephrectomy was followed shortly by death from cerebrovascular insufficiency; in the other, nephrectomy, after unsuccessful conservative measures, was followed by significant improvement. In 2 cases the degree of arterial stenosis was found at operation to be insignificant.

Renal arterial stenosis may be congenital or acquired, and may give rise to significant hypertension. The suspected clinical diagnosis may be strengthened by arteriographic demonstration of renal arterial stricture. At operation the

diagnosis is confirmed by demonstration of a significant drop in arterial pressure across the stenotic segment. Whenever possible, surgical arterial reconstruction with conservation of the kidney is indicated, since the kidney itself is frequently normal and may well be the better of the 2 kidneys. If conservative surgical treatment is impossible or the kidney is seriously damaged, nephrectomy is indicated.

REFERENCES

1. Adams, L. J., Notkin, M., and Pritchard, J. E.: Hypertension in Two Cases of Renal Artery Occlusion, Canad. M. A. J. **64**: 224, 1951.
2. Arnold, M. W., Goodwin, W. E., and Colston, J. A. C.: Renal Infarction and Its Relation to Hypertension, Urol. Survey **1**: 191, 1951.
3. Bahnson, H. T., Cooley, R. N., and Sloan, R. D.: Coarctation of the Aorta at Unusual Sites. Report of Two Cases With Angiocardiographic and Operative Findings, Am. Heart J. **38**: 905, 1949.
4. Baron, G. J., and Koenemann, R. H.: Arteriovenous Fistula of the Renal Vessels. A Case Report, Radiology **64**: 85, 1955.
5. Bauer, H., and Forbes, G. L.: Unilateral Renal Artery Obstruction Associated With Malignant Nephrosclerosis Confined to the Opposite Kidney, Am. Heart J. **44**: 634, 1952.
6. Blahd, W. H., Marcus, R., and Wasserman, D. M.: A Case of Malignant Hypertension Secondary to Renal Ischemia, Ann. Int. Med. **37**: 179, 1952.
7. Blalock, A., and Levy, S. E.: Studies of the Etiology of Renal Hypertension, Ann. Surg. **106**: 826, 1937.
8. Bourne, W. A.: Nephrectomy in Hypertension Due to Renal Artery Infarction With Superinfection of Streptococcal Endocarditis, Brit. M. J. **2**: 271, 1954.
9. Burkland, C. E.: Apparent Cure of Hypertension by Nephrectomy, J. Urol. **46**: 638, 1941.
10. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Invest. **16**: 889, 1937.
11. Collins, H. A., Langa, A. M., Olsen, N. S., and Scott, H. W., Jr.: Further Studies of the Renal Factor in the Hypertension of Experimental Coarctation of the Aorta, Proc. Surg. Forum, Clin. Congress, Am. Coll. Surgeons **4**: 126, 1954.
12. Cornwell, P. M.: Hypertension Due to Partial Renovascular Occlusion. Report of a Case, New England J. Med. **241**: 1006, 1949.
13. Davson, J.: Malignant Hypertension Associated With Hydatid Disease of the Kidney, J. Path. & Bact. **53**: 207, 1941.
14. Decamp, P. T., Snyder, C. H., and Bost, R.: Severe Hypertension Due to Congenital Stenosis of Artery to Solitary Kidney Corrected by Splenorenal Arterial Stenosis, A. M. A. Arch. Surg. In press.
15. Ehrlich, A., Brodoff, B. N., Rubin, I. L., and Berkman, J. I.: Malignant Hypertension in a Patient With Renal Artery Occlusions, A. M. A. Arch. Int. Med. **92**: 591, 1953.
16. Farrell, J. I., and Young, R. H.: Hypertension Caused by Unilateral Renal Compression, J. A. M. A. **118**: 711, 1942.
17. Fishberg, A. M.: Hypertension Due to Renal Embolism, J. A. M. A. **119**: 551, 1942.
18. Fisher, E. R., and Corcoran, A. C.: Congenital Coarctation of the Abdominal Aorta With Resultant Renal Hypertension, A. M. A. Arch. Int. Med. **89**: 943, 1952.
19. Freeman, N. E., Leeds, F. H., Elliott, W. G., and Roland, S. I.: Thromboendarterectomy for Hypertension Due to Renal Artery Occlusion, J. A. M. A. **156**: 1077, 1954.
20. Frelick, R. W., and Shellenberger, W. D.: Abdominal Aortic Thrombosis Producing a Goldblatt Kidney, Delaware M. J. **26**: 260, 1954.
21. Goldblatt, H.: The Renal Origin of Hypertension, Physiol. Rev. **27**: 120, 1947.
22. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**: 347, 1934.
23. Goodman, H. L.: Malignant Hypertension With Unilateral Renal Artery Occlusion, New England J. Med. **246**: 8, 1952.
24. Griffiths, A. L.: Hypertension of Renal Origin in Childhood, Arch. Dis. Childhood **25**: 81, 1950.
25. Harris, J. S., Sealy, W. C., and DeMaria, W.: Hypertension and Renal Dynamics in Aortic Coarctation, Am. J. Med. **9**: 734, 1950.
26. Harrison, R. C., and Alton, J. D. M.: The Renal Factor in the Hypertension of Experimental Coarctation of the Aorta, Proc. Surg. Forum, Clin. Congress, Am. Coll. Surgeons **5**: 146, 1955.

27. Hoffman, B. J.: Renal Ischemia Produced by Aneurysm of Abdominal Aorta, J. A. M. A. **120:** 1028, 1942.
28. Howard, J. E., Berthrong, M., Gould, D. M., and Yendt, E. R.: Hypertension Resulting From Unilateral Renal Vascular Disease and Its Relief by Nephrectomy, Bull. Johns Hopkins Hosp. **94:** 51, 1954.
29. Howard, T. L., Forbes, R. P., and Lipscomb, W. R.: Aneurysm of the Left Renal Artery in a Child Five Years Old With Persistent Hypertension, J. Urol. **44:** 808, 1940.
30. Hurwitt, E. S., Seidenberg, B., Haimovici, H., and Abelson, D. S.: Splenorenal Arterial Anastomoses, Circulation **14:** 532, 1956.
31. Imber, I., and Clymer, R. H., Jr.: Obstruction of the Renal Artery Producing Malignant Hypertension, New England J. Med. **252:** 301, 1955.
32. Julian, O. C., Dye, W. S., Jr., Olwin, J. H., and Jordan, P. H.: Direct Surgery of Arteriosclerosis, Ann. Surg. **136:** 459, 1952.
33. Laforet, E. G.: Malignant Hypertension Associated With Unilateral Renal Artery Occlusion. Three Cases, Ann. Int. Med. **38:** 667, 1953.
34. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39:** 611, 1938.
35. Malisoff, S., and Macht, M. B.: Thrombo-angiitic Occlusion of the Renal Artery With Resultant Hypertension, J. Urol. **65:** 317, 1951.
36. Margolin, E. G., Merrill, J. P., and Harrison, J. H.: Diagnosis of Hypertension Due to Occlusions of the Renal Artery, New England J. Med. **256:** 581, 1957.
37. Oppenheimer, B. S., Klemperer, P., and Moschkowitz, L.: Evidence for the Goldblatt Mechanism of Hypertension in Human Pathology, Tr. A. Am. Physicians **54:** 69, 1939.
38. Owen, W. F., Jr., and Pearlman, C. K.: Hypertension Due to Thrombosis of the Renal Artery. Report of a Case in Which a Cure Was Obtained by Nephrectomy, J. Urol. **68:** 11, 1952.
39. Pastor, B. H., Myerson, R. M., Wohl, G. T., and Rouse, P. V.: Hypertension Associated With Renal Artery Aneurysm and Relieved by Nephrectomy, Ann. Int. Med. **42:** 1122, 1955.
40. Perry, C. B.: Malignant Hypertension Cured by Unilateral Nephrectomy, Brit. Heart J. **7:** 139, 1945.
41. Poutasse, E. F.: Occlusion of a Renal Artery as a Cause of Hypertension, Circulation **13:** 37, 1956.
42. Poutasse, E. F., and Dustan, H.: Urologic Causes of Hypertension. I. Hypertension Due to Renal Artery Lesions, Cleveland Clin. Quart. **23:** 3, 1956.
43. Poutasse, E. F., Humphries, A. W., McCormack, L. J., and Corcoran, A. C.: Bilateral Stenosis of Renal Arteries and Hypertension Treated by Arterial Homografts, J. A. M. A. **161:** 419, 1956.
44. Price, R. K., and Shelton, R.: Hypertension Due to Syphilitic Occlusion of the Main Renal Arteries, Brit. Heart J. **10:** 29, 1948.
45. Riggs, T. F., and Satterthwaite, R. W.: Unilateral Kidney With Partial Occlusion of the Renal Artery Associated With Hypertension. Case Report, J. Urol. **45:** 513, 1941.
46. Rob, C.: Place of Direct Surgery in Treatment of Obliterative Arterial Disease, Brit. M. J. **2:** 1027, 1956.
47. Ronald, J., and Leslie, M.: Thrombosis of the Abdominal Aorta, With Report of a Case, Glasgow M. J. **134:** 7, 1940.
48. Rytand, D. A.: The Renal Factor in Arterial Hypertension With Coarctation of the Aorta, J. Clin. Invest. **17:** 391, 1938.
49. Saphir, Otto, and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66:** 541, 1940.
50. Schaffer, A. J., and Markowitz, M.: Hypertension Treated by Nephrectomy. A Report of 4 Additional Cases and a Re-evaluation of Prognosis and Criteria for Operation, Am. J. M. Sc. **227:** 417, 1954.
51. Scott, H. W., Jr., and Bahnson, H. T.: Evidence for a Renal Factor in the Hypertension of Experimental Coarctation of the Aorta, SURGERY **30:** 206, 1951.
52. Scott, H. W., Jr., Collins, H. A., Langa, A. M., and Olsen, N. S.: Additional Observations Concerning the Physiology of the Hypertension Associated With Experimental Coarctation of the Aorta, SURGERY **36:** 445, 1954.
53. Silvis, R. S., Hughes, W. F., and Holmes, F. H.: Aneurysm of the Renal Artery, Am. J. Surg. **91:** 339, 1956.
54. Smith, H. W.: Unilateral Nephrectomy in Hypertensive Disease, J. Urol. **76:** 685, 1956.
55. Snyder, C. H., Bost, R. B., and Platou, R. V.: Hypertension in Infancy With Anomalous Renal Artery, J. Pediat. **15:** 88, 1955.

56. Stewart, C. F.: Arteriosclerosis of the Renal Artery Orifices With Severe Hypertension, J. A. M. A. 114: 2099, 1940.
57. Thompson, J. E., and Smithwick, R. H.: Human Hypertension Due to Unilateral Renal Disease, With Special Reference to Renal Artery Lesion, Angiology 3: 493, 1952.
58. Wainwright, J.: Hypertension Following Renal Infarction, Lancet 1: 62, 1949.
59. Yuile, C. L.: Obstructive Lesions of the Main Renal Artery in Relation to Hypertension, Am. J. M. Sc. 207: 394, 1944.

Discussion

DR. NORMAN E. FREEMAN (San Francisco, Calif.).—We have had 6 cases in all in which there has been some type of renal artery involvement associated with thrombotic conditions in the aorta. (Slide.) This is a patient who developed occlusion of the aorta at the age of 39 while still in the armed forces. He even had had a myelogram performed and was discharged from the service as a neurotic with pain in the back and legs. He went on for a period of 6 years and then developed severe hypertension. At that time Dr. Ogaard of Sacramento thought the occlusion of the aorta might have extended upward. Aortography shows very clearly the stenotic area at the orifice of the left renal artery. The second picture shows the persistence of dye in the renal artery indicating marked impairment of arterial circulation. That was in 1952. In 1954, the next slide shows the artery completely restored. There is marked decrease in the size of the marginal artery which is frequently found after a successful endarterectomy. He has been followed for 3 years more and has remained symptom free. He came back again because of occlusion of the left iliac. A graft was put in and he is still in good condition 6 years after the first operation.

The last slide is that of a patient a year ago who had absence of the left kidney and stenosis of the right renal artery. We performed a thromboendarterectomy and then through a transverse incision in the renal artery using a Pott's ductus clamp on the proximal end of the renal artery with pressure temporarily applied to the aorta, the occluding material was removed.

I mention these cases because we have had unfortunate results in 3 cases where we tried to curette out the grumous material from the aorta from below and have accidently pushed a plaque into the orifice of one of the renal arteries. One patient developed severe hypertension which responded to nephrectomy. Another patient, after an unsuccessful operation, finally acquired anuria 3 years later. The aorta and renals were completely occluded. We had one more patient with an unsuccessful thromboendarterectomy who developed severe hypertension a year after the first operation. He was followed for 18 months and suddenly dropped dead of a coronary. At autopsy there was organized thrombosis of the aorta all the way to the celiac axis. He was getting some circulation to the kidneys through the collaterals. Of course, he had had long-term hypertension.

DR. JESSE E. THOMPSON (Dallas, Tex.).—It is very important to diagnose unilateral renal disease in a hypertensive patient as this type of hypertension may be curable. Patients with parenchymal renal disease respond poorly to surgery whereas those with renal artery disease respond in a very dramatic fashion. Aortograms are important in the diagnosis, and every effort should be made to save the kidney. If this is not possible, nephrectomy will effect a cure. I should like to show you 2 cases. Both had hypertension due to unilateral renal artery disease and both were relieved following nephrectomy. Both of these patients were in their 30's. One had a blood pressure of 191/132 and the other 229/130. Both had hemorrhages and exudates in the eyegrounds and abnormal electrocardiograms. One was found to have an arteriosclerotic occlusion of the left renal artery and the other had a thrombosed aneurysm of the right renal artery. Nephrectomy was performed in both cases. (Slides.) As you see, blood pressure returned to normal levels in both patients, and their eyegrounds reverted to normal as did the electrocardiograms. Since this is a curable form of hypertensive disease, it is of the utmost importance that all efforts be made to diagnose the renal vascular lesions so that appropriate surgery may be carried out.

DR. A. W. HUMPHRIES (Cleveland, Ohio).—I agree in every respect with the material given. The supplementary material we have to offer actually belongs to Dr. Eugene Poutasse of the Department of Urology of the Cleveland Clinic who is doing the majority of the work in some of the renal forms of hypertension. We have 42 patients with demonstrable renal arterial stenotic disease. I believe the only method of accurate diagnosis is aortography and we are performing aortograms in all patients under 35 who have hypertension, all patients who have pre-existing hypertension who suddenly get worse, all patients with hypertension unimproved by medical regime, and all patients in whom hypertension follows an attack of flank pain. Four of the 42 patients were seen in 1953 and 1954 and were inadequately worked up. Eight have been seen during the course of this current year and are too recent to consider. Of the remaining 30, eight of these patients are less than 35 years of age. Twenty-two of the cases are unilateral, of which 11 showed a normal urogram and 11 showed an abnormal urogram of some degree. Eight of the cases showed bilateral renal artery stenosis. Of these 30, 11 are maintaining a constant blood pressure which is not of excessive amount and are still being followed on a medical regime. Nineteen of the patients with progressive hypertension of recent origin were operated upon. The results in all but one of these recent cases are favorable. Fourteen had a unilateral nephrectomy. One had a thromboendarterectomy. One had a transaortic dilatation and 4 have had arterial grafts. There are 7 who have been followed for more than one year. Of these, 5 have a normal blood pressure and 2, although they do not have normal blood pressures, had a malignant hypertension at the time they were done which has since been reversed. Ten have been followed for less than one year and, of these, 6 show a normal blood pressure and 4 have a markedly improved blood pressure. Of special interest in this group are the ones who had arterial grafts. One was in a 15-year-old boy with bilateral renal artery disease. He is now 19 months postoperative and is maintaining a normal blood pressure. Two others were unilateral, one of whom died postoperatively as a result of rupture of the anastomotic line between the renal artery graft and the aorta. This case points out the inadvisability of performing an end-to-side anastomosis to a markedly sclerotic host vessel. The most recent graft was bilateral and is only 2 months postoperative. Although the patient's diastolic pressure has decreased 15 mm. and appears to be quite successful, it is much too early to evaluate this case. I would like to stress the desirability of performing aortograms on all suspicious cases of hypertension.

DR. PAUL T. DE CAMP (closing).—The discussion has added so much in the way of clinical information to our small series. I appreciate the remarks about renal endarterectomy. We have tried one through a longitudinal incision in the renal artery; this failed. We were going into the aorta, but, in view of Dr. Freeman's remark, a transverse incision in the renal artery is indicated. One thing we feel rather strongly about is that we are very anxious that there be no return of the stenosis. (Slide.) The splenic artery is long and redundant. It lies very close to the left renal artery. Incidentally, the same is true of the splenic vein and left renal vein, and, since we have had some experience now in swinging down the splenic artery, I am going to try it on a vein for splenorenal shunt in portal hypertension. (Slide.) Here as you see is another case of renal arterial stenosis. This splenic artery comes off low and is very redundant. It is very simple to divide this and bring it down as an anastomosis. A longitudinal midline incision is used. The spleen does not need to be removed.

ADDENDUM

The 4 surviving patients have continued to improve during the ensuing 6 months since this report was written. Three additional patients have had conservative vascular reconstruction with gratifying results. One of these, a young adult, had splenorenal arterial shunt for congenital stenosis of the left renal artery with gratifying results. The other 2 were older patients with arteriosclerotic plaques, which were successfully treated by endarterectomy.

OBSERVATIONS ON THE PATHOGENESIS AND MANAGEMENT OF MASSIVE VENOUS OCCLUSION

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UNLIKE the usual mild case of acute thrombophlebitis of the leg veins, an occasional patient will develop a much more extensive thrombotic process which may endanger both his limb and his life. This entity, first described by Fabricus Hildanus in 1593[9] and later by Gregoire in 1938,[10] has been called "phlegmasia cerulea dolens," "pseudoembolic phlebitis," and, lately by Veal,[26] "massive venous occlusion."

This latter term seems most appropriate in describing the variety of signs and symptoms of this syndrome. Onset of this process may be slow or very rapid and may follow a smoldering phlebitis of the more frequent type or may develop suddenly in an ambulatory patient. Severe pain, tense edema, and bluish skin discoloration of the leg and thigh characterize this process. The foot becomes cold, peripheral pulses in the involved extremity may diminish then disappear, and gangrene has followed in about half the reported cases. Hypotension and a shocklike state have been reported frequently, and a fatal outcome is not unusual.

Both the pathogenesis and most satisfactory treatment have caused considerable controversy. Extensive iliofemoral venous thrombosis is undoubtedly the most important pathologic change causing the severe symptoms. Debate centers around the cause of disappearance of pulses and the origin of tissue necrosis. It is felt by some that intense arterial spasm from reflexes originating in the adjacent involved veins causes the decreased arterial flow and absent pulses. Others have felt that arterial inflow is diminished by complete obstruction of the venous channels of the entire leg. Some have mentioned venous spasm as an additional factor in outflow obstruction.

A uniformly efficient method of relief has not yet evolved and several therapeutic approaches have been advocated. Lumbar sympathetic nerve block for relief of arterial spasm has been recommended by many.[14, 19, 21] This has produced rapid improvement in some but not all cases. Veal[26] reported 9 cases treated by high elevation of the legs with rapid passive flexion of the knee and hip until edema begins to subside. Results were impressive in this group of cases. Mahorner[15] has suggested immediate thrombectomy of the iliac or femoral vein, thus removing the venous obstruction. Heparin is then used to prevent recurrent thrombosis of this venous segment. Even proximal venous ligation has been proposed but the rationale of this maneuver is uncertain. Anlyan[1] has recently postulated that heparin alone is adequate therapy, acting by neutralizing the vasoconstrictor factor of serotinin.

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In an effort to gain further information concerning pathogenesis and therapeutic effectiveness of various measures, continuous venous pressure studies of the involved and uninvolved legs have been carried out on patients with massive venous occlusion before and after several methods of therapy.

Even in experienced hands, the proper disposition of Novocain in the region of the lumbar paravertebral ganglia is often uncertain. Therefore, spinal anesthesia has been used as a nerve block in these patients. A more certain and complete block is obtained, and the additional advantage of complete relief of pain is obtained.

CASE REPORTS

CASE 1.—R. S. was admitted to Birmingham Veterans Administration Hospital, Jan. 9, 1954. This 36-year-old white man was well until the day before admission when he noticed the acute onset of mild left lower back pain which did not necessitate bed rest or medication. Five hours before admission, while walking at his natural pace he suddenly developed pain, swelling, tenseness, and discoloration of his left lower extremity. The pain was a dull ache involving the entire extremity to the groin and the skin developed a bluish discoloration with scattered red petechiae. The leg was cold below the knee. The left femoral pulse was normal; the popliteal and posterior tibial pulses could not be felt. The dorsalis pedis was palpable but somewhat diminished. All pulses were normal on the right. The left leg was one inch larger in circumference at the calf and mid-thigh than the right. The left saphenous vein was distended and tense at the ankle; venous pressure in this vein with the patient supine was 410 cm. H_2O. Venous pressure in the right saphenous was 130. Physical examination was otherwise negative. Laboratory tests showed WBC 18,000, hemoglobin 17 Gm., and clotting time 7 minutes. A spinal anesthetic was immediately carried out with 12 mg. Pontocaine, obtaining an anesthetic level at the costal margin. There was no significant drop in blood pressure. Within 15 minutes of introducing the anesthetic the left leg became pinker and warmer, a bounding posterior tibial pulse appeared, and the dorsalis pedis became stronger. The legs were elevated and one hour later the color was much improved. The patient was started on heparin 100 mg. every 4 hours. Several hours after the spinal anesthetic, as sensation was returning, the venous pressure measurement was repeated again with the patient supine. Pressure in the left saphenous had fallen to 320 cm. H_2O and the vein felt much less tense. For the next 2 weeks he was treated by high elevation of his legs and maintenance of his clotting time between 20 and 30 minutes with heparin every 4 hours intramuscularly. Despite this, pain gradually became worse, the leg became more swollen, and the patient developed distended veins over his lower abdomen. Two weeks after admission, pressure in his left saphenous vein was 550 cm. H_2O, pulses were palpable, and the leg was warm. After omitting heparin for 12 hours to allow his clotting time to return to normal, a second spinal anesthetic was given with immediate improvement and a softening of the tenseness of the left saphenous vein. He was immediately put back on heparin. The leg rapidly lost its swelling in the next few days and tenderness in the calf slowly disappeared. Three weeks after admission it was noted that the right leg was edematous at the ankle and there was moderate tenderness and pain along the course of the vein in the right groin and thigh again developing while on adequate heparin therapy. This gradually improved in the following week and the patient became symptom free 4 weeks after admission. Heparin was continued for 2 weeks, then gradually discontinued as the patient became ambulatory with elastic support. He was discharged 2 months after onset. Three months after admission he still had considerable edema in both ankles on walking even with firm elastic support from toe to knee and was not able to stand for any length of time.

Comment.—This was the first case in which dramatic improvement was observed after spinal anesthesia and only 2 venous pressure determinations were

made several hours apart. Because of the incomplete pressure information obtained, a plan of continuous venous pressure observation was outlined for subsequent cases. In this case the major improvement occurred before heparin was started, and adequate heparinization did not prevent recurrence of massive occlusion.

CASE 2.—Mrs. D. W. was a 28-year-old white woman admitted to University Hospital Sept. 16, 1956, 2 weeks post partum.

While standing cooking breakfast she felt a sudden pain in her left calf that almost caused her to fall. In 10 minutes the leg began to turn blue and cause extreme pain. Past history revealed milk leg on the left after the first of 5 pregnancies 10 years previously. During her recent pregnancy she had noted increased swelling in the left leg.

On examination the left leg was cyanotic to the hip with tense edema up to the gluteal cleft. She could barely move her toes and pressure on the calf or inner thigh gave considerable pain. The entire left leg was cold and pulseless; even the left femoral was absent. The right leg was normal and all pulses were present. Blood pressure on admission was 80/60 and she was weak and lethargic.

Shortly after admission polyethylene catheters were inserted into the long saphenous veins at both ankles and connected to infusion bottles. Initial venous pressure measurements were 90 cm. H_2O in the right leg and 934 cm. H_2O in the left. Approximately 6 hours after onset of symptoms spinal anesthesia was produced with 12 mg. of Pontocaine with the patient remaining supine during pressure measurements but the legs elevated 8 inches between measurements. Her left leg venous pressure slowly fell to 465 in the next 9 hours. Heparin was added to the infusion bottle (200 mg. heparin/1,000 c.c. glucose and water) and this was allowed to run at 30 drops per minute into the left saphenous catheter (Table I). She was kept on a constant heparin drip for one week and on intramuscular heparin for another 5 days. During this time she was kept at complete bed rest with legs elevated. The patient was discharged after 2 weeks and 3 months later was having only minimal edema after a day's housework wearing Ace bandage support.

TABLE I. PROTOCOL ON MRS. D. W. (CASE 2)

		VENOUS PRESSURE (CM. H_2O)		
	TIME	RIGHT LEG	LEFT LEG	REMARKS
9/16/56	1:45 P.M.	90	995	Immediately prior to spinal
	2:30	90	875	30 minutes after spinal
	3:00	90	865	Heparin drip started
	3:15	90	805	
	3:30	90	770	
	3:45	90	770	
	4:00	90	750	
	4:30	90	675	
	5:00	90	640	
	6:00	90	620	Pedal pulses returned
	7:00	90	580	
	8:00	90	530	
	10:00	90	495	Leg warm, less tense
	11:00	90	465	Clotting time 24 minutes

CASE 3.—Mrs. S. W., a 56-year-old woman, was readmitted to the University Hospital, Oct. 6, 1956, 6 days after discharge following a left hemimandibulectomy and left radical neck dissection for carcinoma of the alveolar ridge. Her convalescence had been uncomplicated and there had been no evidence of phlebitis. She awakened early on the morning of readmission with a sudden pain in the right medial thigh which rapidly became intense, and she noted the right leg was swollen and blue.

On admission examination 2 hours later her blood pressure was 100/78, pulse rate 110, and respiratory rate 22. She had no chest pain or changes in breath sounds to auscultation. Her right leg was markedly edematous and tense up to the groin and was mottled blue. This limb was colder than the left, the femoral pulse on the right was quite weak compared to the left, and no popliteal or pedal pulses could be felt on this right side.

Immediately after admission large bore polyethylene catheters were inserted into the long saphenous vein of both ankles, and venous pressure was measured with the patient supine in bed. In the normal leg venous pressure measured 30 cm. H_2O, whereas in the edematous leg it measured 950 cm. H_2O. Spinal anesthesia was produced 6 hours after onset, using 12 mg. of Pontocaine. Arterial pressure dropped to 75/40 in a few moments but was restored to 160/100 with Vasoxyl and stabilized in 30 minutes at 100/80. With the patient still supine, venous pressure was recorded intermittently in the right leg for 11 hours. As shown in Table II, the protocol of her progress during this time, her pain was immediately relieved, the mottled blue color diminished in about one hour, and pedal pulses again became palpable. Six hours after the spinal, sodium heparin 120 mg. was added to the intravenous solution of 5 per cent glucose and water which was allowed to drip into the right long saphenous vein at about 20 drops per minute. Five hours after the spinal when the venous pressure in this extremity had dropped to 750 cm. H_2O, the foot of the bed was elevated 8 inches. Subsequent venous pressure determinations were made by temporarily lowering the bed to supine position again. Nine hours after spinal anesthesia venous pressure was 540 cm. H_2O in the right leg and pressures were discontinued. Intravenous heparin was continued by constant drip into the right long saphenous vein for 3 days maintaining her clotting time between 15 and 30 minutes. Intramuscular heparin was continued for 10 days and her leg rapidly improved. She was discharged with minimal edema but wearing Ace bandage. She was readmitted one week later with pleuritic pain in the left lateral chest, rusty sputum, and x-ray evidence of a small pulmonary infarct. She was treated with heparin intramuscularly for 10 days and had no further trouble. Two months later there was no evidence of edema in the right leg even without Ace bandage support.

TABLE II. PROTOCOL ON MRS. S. W. (CASE 3)

		VENOUS PRESSURE		
	TIME	RIGHT LEG	LEFT LEG	REMARKS
10/6/56	1:00 P.M.	560	30	Admission
	1:50	940	30	Immediately prior to spinal
	2:30	950	30	40 minutes after spinal
	2:55	935	30	
	3:30	774	30	
	4:00	754	30	
	6:00	750	30	Foot of bed elevated
	7:00	700	30	Heparin drip started
	8:00	700	30	
	8:30	670	30	
	9:00	600	30	
	9:30	540	30	
	10:30	540	30	
	11:00	540	30	

Comment.—These 2 women patients were admitted shortly after the onset of massive venous occlusion of severe degree with extreme elevation of saphenous venous pressure. Both responded dramatically to a single spinal anesthetic, and the steady fall in venous pressure was closely related to clinical improvement. To test the possibility that heparin contributed to the release of spasm and lowering of pressure in Case 2, this drug was not started in Case 3 for 6 hours after the spinal anesthetic. There was no evidence that heparin accelerated the drop in pressure (Fig. 1).

CASE 4.—Mr. D. S., a 72-year-old man, was admitted to the University Hospital, Jan. 10, 1957, with a 10-hour history of a swollen, tense, painful left leg. Pain developed suddenly on arising that morning and had slowly progressed in severity during the day. One month previously he had had radon seeds implanted in a tumor of the bladder, a possible factor in precipitating his venous occlusion. On admission examination he was cold and clammy, in obvious distress, and the left leg was tense and blue from the groin to toes. The femoral pulse on the left was faintly palpable but no pulses could be felt below this level. The right leg was not swollen and pulses were palpable. His blood pressure was 100/60, pulse 120. Twelve hours after onset he was taken to the operating room and polyethylene catheters were placed in each saphenous vein at the ankle. Venous pressure in the right saphenous measured 50 cm. H_2O, while in the left ankle it was 780 cm. H_2O. Spinal anesthesia was produced with 12 mg. Pontocaine. Thirty minutes later the pressure had fallen to 756 mm. The left common femoral vein was isolated in the groin and thrombectomy was performed through a longitudinal incision. An 8-inch long loose clot was aspirated from above followed by a free flow of blood. The distal clot was then sucked and milked out and found to measure 12 inches in length.

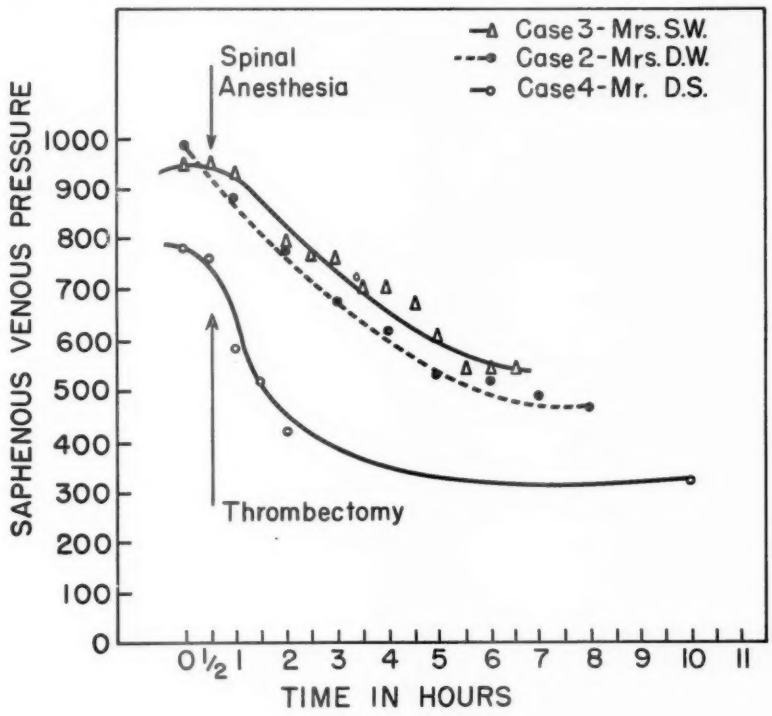

Fig. 1.

Here again, free flow of blood was obtained from below. The longitudinal incision was carefully closed with 5-0 arterial silk with an over-and-over suture to avoid constriction of the vein and flow was then allowed to resume through its normal venous channel. Saphenous venous pressure was found to measure 588 cm. H_2O immediately after this. A constant heparin infusion was started into the left saphenous cannula before the incision was closed and the patient's legs were elevated. Table III shows subsequent pressure recordings. The following morning with his bed level, left saphenous venous pressure measured 319 cm. H_2O which was still considerably above normal. Heparin drip was continued for 48 hours into this vein followed by 8 days of intramuscular heparin. His leg, by the morning after surgery, was dramatically improved, warmer with good pulses, but still somewhat edematous. Edema gradually subsided before discharge and after 2 months he was able to discard supportive wrappings.

TABLE III. PROTOCOL ON MR. D. S. (CASE 4)

TIME	VENOUS PRESSURE	REMARKS
9:00 P.M.	780	In operating room just before spinal
9:30 P.M.	756	20 minutes after spinal
9:45 P.M.	588	5 minutes after thrombectomy
10:25 P.M.	516	Heparin drip running
11:00 P.M.	420	
9:00 A.M.	319	Leg warm, good pulses, still moderate edema

Comment.—This patient, treated by thrombectomy with maintenance of venous continuity as described by Mahorner,[15] showed a dramatic recovery. Saphenous venous pressure dropped precipitously after removal of the clot but not back to normal. The lower level of final venous pressure obtained after thrombectomy as compared with sympathetic block alone may be only a reflection of a less severe obstruction in Case 4 as suggested by a lower initial venous pressure (Fig. 1).

CASE 5.—Mr. E. G., a 40-year-old farmer, was admitted to the Birmingham Veterans Administration Hospital March 10, 1954. Six weeks earlier he had sustained peppering gunshot wounds of both anterior thighs with a 410 shotgun, a mild injury in this case which did not require hospitalization. Four weeks later he developed swelling, pain, and increased warmth in the left calf. The following day while in bed he experienced a sharp stabbing pain in the right anterior chest followed by severe dyspnea. He was hospitalized elsewhere and given oxygen. Two days later he coughed up a cupful of dark blood. A second episode of left anterior chest pain occurred 5 days later, less severe than the first. He was transferred to the Veterans Administration Hospital 2 weeks after the second episode and there was started on Dicumarol. Five days after admission despite a prolongation of prothrombin time to 21 seconds (control 12 seconds), he developed massive venous occlusion of the previously uninvolved right leg. This extremity became tensely swollen to the groin and a mottled blue, with marked tenderness of the thigh and right lower abdomen. Several hours after onset the femoral and pedal pulses were still palpable and the leg warm. Both legs were elevated to 45 degrees and passive flexion of the knee and thigh was begun. Almost immediately he developed a severe stabbing pain in the left lateral chest, a previously painless area, and became severely dyspneic and slightly cyanotic. Flexion was stopped at once and oxygen started. There was gradual improvement in his chest symptoms in the next few hours and the next morning he was much better. Chest x-ray showed a wedge-shaped area in the lingula on the left of presumed new infarction. He was placed on intramuscular heparin and his clotting time was kept at about 30 minutes for the next 2 weeks. Several months later he was ambulatory with mild postphlebitic edema easily controlled with Ace bandages.

Comment.—This patient demonstrated the possibility of precipitating pulmonary embolism by vigorous passive exercise of the extremity, the procedure recommended by Veal.[26] Other less dangerous measures would therefore seem preferable.

DISCUSSION

The most interesting and controversial feature of massive venous occlusion of the lower extremities is the cause of gangrene that develops in about half of these cases if untreated. Haimovici[11] has expressed the view that a complete blockage of venous return by thrombosis is an essential prerequisite for the occurrence of gangrene. In support of this view, cases are reported in which

gangrene developed in extremities without loss of peripheral pulses. Salmon, Andier, Jouve, and Haimovici[24] have produced anteriograms in amputated extremities showing patency of the entire arterial system. De Souza-Pereira[21] produced wet gangrene in the legs of dogs by division of *all* the veins at the root of the leg. Here, also, arteriograms offered proof of arterial patency and evidence of pure venous origin of gangrene.

On the basis of clinical and experimental evidence, Leriche and Kunlin[14] and Ochsner and DeBakey[19] postulated that many of the clinical manifestations in venous thrombosis are due to vasospasm of the arterial and venous systems and that the vasoconstricting impulses originate in the involved venous segment. DeBakey, Burch, and Ochsner[3, 5] noted a 50 per cent reduction in the pulse volume of the hindpaw of dogs after chemical irritants were injected into an isolated femoral vein segment. This reduction in pulse volume could be prevented by prior ipsilateral sympathectomy or by perivascular infiltration of procaine hydrochloride. This would certainly seem to be good evidence for reflex arterial spasm arising in the inflamed vein and mediated through the lumbar sympathetic nerves. Also, however, Burch, DeBakey, and Sodeman[3] found that simple ligation of the dog's femoral vein caused a rise in venous pressure to 13 times the normal value and a diminution of paw pulse volume to 50 per cent of the control level. This they studied further in isolated arterial segments which demonstrated a gradual decrease in pulse volume as intraluminal pressure was increased. In other words, one explanation of the reduced pulses in patients with massive venous occlusion may be the increased distention and reduction in elasticity of the arteries, secondary to venous outflow obstruction.

Pereira[21] showed by phlebograms in phlebitis that the caliber of veins increased considerably after lumbar sympathetic block or after Novocain drip into the inflamed vein. We believe that the gradual fall in venous pressure following spinal anesthesia in the cases reported here offers additional evidence that venous spasm is a contributory factor in producing total outflow occlusion in the legs affected by massive venous occlusion. Whether or not arterial spasm occurs cannot be determined by this study. Release of arterial spasm by sympathetic blockade would cause a rise in venous pressure rather than a fall, if venous obstruction remained the same. Previous work from this laboratory has shown a rise in walking venous pressure after arterial vasodilatation in chronic venous disease.[7] Arterial spasm, if present, may be a desirable and protective mechanism preventing further sequestration of blood in the extremity. The fact that our 3 patients treated with sympathetic block and heparin recovered without loss of limb suggests that release of venospasm may tip the scales favorably toward recovery.

Of very great importance, however, is the necessity of knowing not only what will occasionally produce relief but what is the ideal therapy both from the standpoint of immediate salvage of life and leg, as well as long-term freedom from venous incompetency. What therapy is least likely to result in a postphlebitic leg yet affords adequate protection against pulmonary emboli?

Veal's method of leg elevation and rapid flexion undoubtedly opens venous channels and reduces edema but is dangerous in the presence of loosely attached thrombi. Our experience with this method was frightening and demonstrated its dangers. Of the 9 patients reported by Veal, 5 had had previous major vein ligation, which may have protected them from emboli.

A different approach is thrombectomy, removing as much clot as possible from the iliac and femoral veins. This is certainly a more direct approach to the problem but there are certain unanswered questions. Should the femoral vein be ligated following thrombectomy, or should an effort be made to suture the venous incision and maintain venous patency as advocated by Mahorner? One of the cases reported by DeBakey and Ochsner[6] and cases subsequently reported by Ellis and Windham[8] were successfully relieved by thrombectomy soon after the onset of symptoms, followed by femoral vein ligation. How can one explain the benefit obtained when the venous channel is ligated? The most likely explanation is opening of numerous venous collaterals above and below the point of ligation by removing the extensive clot. Only time will allow an evaluation of Mahorner's suggestion that even better results can be obtained by maintaining venous patency. Whether this method may allow the passage of emboli and whether the incidence of postphlebitic edema is decreased are important observations that must be made in a larger group of cases. Our single case treated in this fashion was very satisfactory from the standpoint of rapid relief of venous obstruction and complete recovery without stasis edema. The final venous pressure measurement, however, in this patient indicated that all of the venous obstruction was not removed by thrombectomy, leaving potentially dangerous clot in the calf veins. It is also felt that the final saphenous venous pressure level reached after thrombectomy was not significantly lower than after sympathetic block alone.

Anlyan and associates[1] may be quite correct that heparin alone will release venous spasm in many cases. It certainly is indicated to prevent further propagation of clot and further obstruction of collateral pathways. That it is not always dependable in both these areas was indicated in our Case 1 where massive venous occlusion recurred while the patient was well heparinized with a clotting time consistently longer than 20 minutes.

SUMMARY

Massive venous occlusion (phlegmasia cerulea dolens) is a serious form of thrombophlebitis which has frequently resulted in gangrene of the extremity or death from shock.

To gain information as to the cause of disappearance of peripheral pulses and resultant necrosis of the leg, saphenous venous pressure determinations have been made before and for many hours after (1) sympathetic block by spinal anesthesia and (2) thrombectomy.

A consistent gradual decline in venous pressure after sympathetic block is interpreted to indicate release of an important element of venous spasm.

This venous spasm when added to the massive degree of mechanical obstruction by iliofemoral thrombosis may cause total outflow occlusion. Arterial inflow is thereby prevented and tissue necrosis results. Sequestration of large volumes of fluid in the edematous leg precipitates shock.

Three patients with massive venous occlusion were treated successfully by sympathetic blockade from spinal anesthesia, followed by heparin administration. It is postulated that the variable results reported from paravertebral lumbar sympathetic block in this condition may have been due to failure to produce consistently complete sympathetic blockade.

One patient was treated with spinal anesthesia followed by thrombectomy of the iliac and femoral vein. The vein was not ligated. Venous pressure fell more rapidly after thrombectomy than after sympathetic block alone but the total decrease in saphenous venous pressure was not significantly greater than after block.

One patient was treated with leg elevation and rapid passive flexion and extension. Occurrence of an acute pulmonary embolus shortly after this therapy was begun indicated the potential danger of manipulating an extremity with fresh loosely attached venous thrombosis.

Since no single measure seems to be uniformly successful if used alone, a satisfactory plan of therapy would seem to be: (1) sympathetic block by spinal anesthesia, (2) high leg elevation, (3) constant intravenous heparin drip, and (4) thrombectomy if the venous pressure does not drop or symptoms do not rapidly improve with the first 3 measures.

None of the above measures guarantee freedom from pulmonary embolus and this remains a serious problem.

REFERENCES

1. Anlyan, W. G., Isley, J. K., Schauble, J. F., Baylin, G. J., and Postlethwait, R. W.: Laboratory Studies in the Evaluation of Postphlebitic Disease, presented at the International Society of Angiology in New York, June 1, 1957.
2. Bargen, J. A., and Barker, N. W.: Extensive Arterial and Venous Thrombosis Complicating Chronic Ulcerative Colitis, Arch. Int. Med. 58: 17, 1936.
3. Burch, G. E., DeBakey, M. E., and Sodeman, W. A.: Effect of Venous Pressure on Volume Pulsation, Proc. Soc. Exper. Biol. & Med. 42: 858, 1939.
4. Davies, O. G., and Grimes, O. F.: Pseudo-embolic Phlebitis (Phlegmasia Cerulea Dolens). A Report of Two Cases, Am. J. Surg. 86: 480, 1953.
5. DeBakey, M. E., Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of a Venous Segment on Peripheral Pulse Volume, Proc. Soc. Exper. Biol. & Med. 41: 585, 1939.
6. DeBakey, M. E., and Ochsner, A.: Gangrene Associated With Thrombophlebitis, Phlegmasia Cerulea Dolens, SURGERY 26: 16, 1949.
7. Edwards, W. S.: The Effect of Altering Arterial Flow on Ambulatory Venous Pressure in Postphlebitic Extremities, Surg., Gynec. & Obst. 99: 756, 1954.
8. Ellis, J., and Windham, S.: Acute Massive Venous Occlusion in the Lower Extremity, Ann. Surg. 135: 262, 1952.
9. Fabricus Hildanus, G.: De Gangraena et Sphacelo, Cologne, 1593.
10. Gregoire, R.: La phlebite bleue, Presse méd. 46: 1313, 1938.
11. Haimovici, H.: Gangrene of the Extremities of Venous Origin, Circulation 1: 295, 1950.
12. Halligan, Earl J., Costello, John L., and Lewis, Thomas F.: Acute Massive Venous Occlusion of the Lower Extremity, Ann. Surg. 137: 543, 1953.
13. Laufman, H., Martin, W. B., and Tuell, S. W.: The Pattern of Vasospasm Following Acute Arterial and Venous Occlusions, Micrometric Study, Surg., Gynec. & Obst. 87: 641, 1948.

14. Leriche, R., and Kunlin, J.: Traitement immediat des phlebites postoperatoires par infiltration novo cainigue du sympathigue lombaire, Presse méd. **42**: 1481, 1934.
15. Mahorner, H.: A New Method of Management of Thrombosis of Deep Veins of the Extremities: Thrombectomy, Restoration of the Lumen and Heparinization, Am. Surgeon **20**: 487, 1954.
16. Manheimer, L. H., and Levin, Leo. M.: Phlegmasia Cerulea Dolens, Report of Two Cases and Discussion of Pathogenesis, Angiology **5**: 472, 1954.
17. Miles, R. M.: Phlegmasia Cerulea Dolens, Successful Treatment by Vena Cava Ligation, SURGERY **30**: 718, 1951.
18. Oaks, W., and Hawthorne, H.: Pseudo-embolic Phlebitis With Ligation of the Inferior Vena Cava: A Case Report, Ann. Surg. **127**: 1247, 1948.
19. Ochsner, A., and DeBakey, M.: Thrombophlebitis. The Role of Vasospasm in the Production of the Clinical Manifestations, J. A. M. A. **114**: 117, 1940.
20. Osius, Eugene A.: Acute Massive Venous Occlusions, Arch. Surg. **65**: 19, 1952.
21. Pereira, A. DeSousa: The Innervation of the Veins. Its Role in Pain, Venospasm, and Collateral Circulation, SURGERY **19**: 731, 1946.
22. Perlow, S.: Phlegmasia Cerulea Dolens—Massive Venous Thrombosis Associated With Shock, J. A. M. A. **144**: 1257-1258, 1950.
23. Rasmussen, J. A., Potter, S. E., and Best, R. R.: The Management of Acute Massive Venous Occlusion, SURGERY **40**: 387, 1956.
24. Salmon, M., Audier, M., Jouve, A., and Haimovici, H.: Sur un casde gangrene du membre inferieur par thrombose veinease. Sympathectomie peri-arterielle et veineuse (femorales) inefficace. Amputation, Bull. et mém. Soc. de chir. de Marseille **12**: 1, 1938.
25. Tilley, J. H.: Gangrene of the Extremities in Peripheral Thrombophlebitis, Am. J. Obst. & Gynec. **36**: 157, 1938.
26. Veal, J. Ross, Dugan, J. T., Jamison, W. L., and Bauersfeld, R. S.: Acute Massive Venous Occlusion of the Lower Extremity, SURGERY **29**: 355, 1951.

DISCUSSION

DR. EUGENE A. OSIUS (Detroit, Mich.).—We have been interested for some time in this subject and saw our first case in 1941, which followed cystoscopy. Thrombectomy was used but was unsuccessful. The patient presented all of the classic signs, including loss of pulses, and we operated upon him with the original diagnosis of arterial embolus. However, at operation it was discovered that the entire venous system of the extremity including the iliacs was completely blocked with thrombus, and we were unable to free this thrombus from the vessels. The patient spent 3 months in the hospital, where he ran the gamut of everything and its complications, much to the dismay of myself and my associates, but he eventually made a complete recovery and died later of other causes not related to this illness.

The next case was a patient awaiting operation for carcinoma of the cecum. This patient was immediately thrombectomized and made an excellent recovery. The third case occurred in a patient who was sleeping and occurred for no known reason whatsoever. The fourth one (slide) was a man preparing breakfast for his wife when he had a sudden pain in his extremity. He went into shock and was hospitalized, and a diagnosis of arterial embolus was made. He was transferred to us, but when he saw him the leg was (as noted on the slide) intensely swollen, purplish in color, rather cool to the touch, with edema that was hard and firm, but the pulses had returned. This, of course, gave us the clue that this was an acute massive venous occlusion. He was taken to the operating room and a thrombectomy was performed. The following slide shows the leg immediately after operation, while the patient was still on the table. A definite organized clot was removed from the iliac vein, as shown on the slide, and the patient was later given anticoagulants and general supportive measures. He made an excellent recovery as can be seen on the next 2 slides, which reveal a return of the leg to practically normal proportions within a week to 10 days. The last slide shows the patient 4 months after the incident with a practically normal extremity. One and one-half to two years later, he developed a carcinoma of the descending large bowel.

We believe that the important pathology is the acute sudden onset and the sudden change in the hemodynamics when the iliac or femoral vein is suddenly blocked. It is our feeling that this clot is often already formed or well along in its formation in regard to hours of

duration and does not necessarily form at the time the patient has his first symptom. It has to come from somewhere, and we believe that it may arise from the lower leg. In other words, it is dislodged and again impinged with the resultant catastrophic symptomatology.

Our fifth case was also associated with carcinoma, and we have had 3 or 4 other cases since our first series was reported.

We believe that the incidence as well as the mortality in acute massive venous occlusion is high enough, so that definite attention should be called to this entity and the Profession at large acquainted with its existence. It is our feeling that this is a fit subject for discussion before State and County Societies, as I am quite sure that many cases are being missed and overlooked. It is our conviction that thrombectomy is indicated, should be done, and can be considered safe. This is to be followed by the usual supportive and secondary measures, including subsequent support for the extremity itself, as well as the immediate post-operative care. We classify it as an emergency, secondary only to acute hemorrhage, and it should be so treated.

PREVENTION OF CARDIAC DILATATION AND CEREBRAL HYPERTENSION DURING THORACIC AORTIC OCCLUSION

W. G. Gobbel, Jr., M.D., J. B. Dalton, M.D., R. I. Carlson, M.D., J. M. Merrill, M.D., and H. W. Scott, Jr., M.D., Nashville, Tenn.

(From the Surgical Service, Thayer Veterans Administration Hospital, and the Department of Surgery, Vanderbilt University School of Medicine)

MARKED cerebral hypertension and rapid cardiac dilatation with resultant arrest have at times been an insurmountable problem when the thoracic aorta is cross-clamped for repair of a thoracic aneurysm or for the insertion of a Hufnagel valve. Erlanger and Gasser[5] in experiments carried out in dogs found that the carotid arterial pressure immediately and markedly increased following thoracic aortic occlusion and remained elevated for the periods of observation which were up to 2 hours. Blalock[3] in similar experiments found that oxygen consumption began to decrease immediately following occlusion of the thoracic aorta. He also found that cardiac output decreased and pulse rate increased during the occlusion. Barcroft[1] observed an increase in pressure in the brachiocephalic artery immediately following the simultaneous occlusion of the thoracic aorta and the inferior vena cava above the diaphragm. However, the periods of occlusion and pressure observations were always less than one minute. More recently, Beattie and co-workers[2] in studying effects of hypothermia on spinal cord survival observed a precipitous rise in both the systolic and diastolic arterial pressures above the site of thoracic aortic occlusion in the normothermic dog. These precipitous elevations in blood pressure above the site of occlusion were also observed in dogs whose body temperatures were lowered to 30° C. The experiments reported here were performed primarily in order to determine whether a method could be devised for maintaining relatively normal blood pressures above the site of thoracic aortic occlusion and avoiding cardiac dilatation.

EXPERIMENTAL METHODS AND RESULTS

Seventeen normothermic adult mongrel dogs were used in these experiments. Each dog was anesthetized with intravenous pentobarbital and polyethylene catheters were then introduced into the right common carotid and right femoral arteries These catheters were attached to an electromanometer to record pressures. Similar catheters were also placed in the superior and inferior venae cavae for pressure recording. Electrocardiographic electrodes were attached to each extremity and a continuous recording was made. An intratracheal tube was inserted and attached to a mechanical respirator.

The left chest was opened through the sixth intercostal space and the inferior vena cava above the diaphragm was dissected free from the mediastinal

Read at the Eleventh Annual Meeting of the Society for Vascular Surgery, New York, N. Y., June 2, 1957.

pleura. The descending thoracic aorta was freed from the overlying parietal pleura at the level of D_6 so that it could be occluded with a clamp at that level. At this time base line recordings of pulse and blood pressure were made, during which period no manipulations were carried out. After these recordings the following observations were made.

Experiment A. Thoracic Aortic Occlusion Only.—In each of 10 dogs, the descending thoracic aorta at the level of D_6 was cross-clamped with a Glover aortic clamp. The systolic, diastolic, and mean pressures as measured in the right carotid artery precipitously rose (Fig. 1) and the pressure in the right femoral artery fell. The heart rate remained unchanged in some animals and in others it decreased slightly. The heart dilated and remained dilated while the aorta was occluded. After an observation period of 5 to 10 minutes, the clamp was removed and the carotid arterial pressure fell abruptly below the base line of the control period. Simultaneously the heart rate increased, but within 2 minutes in each instance the blood pressure and heart rate returned approximately to their preliminary base line levels. In several other animals with the thoracic aorta occluded, the carotid hypertensive levels were maintained up to 4 hours.

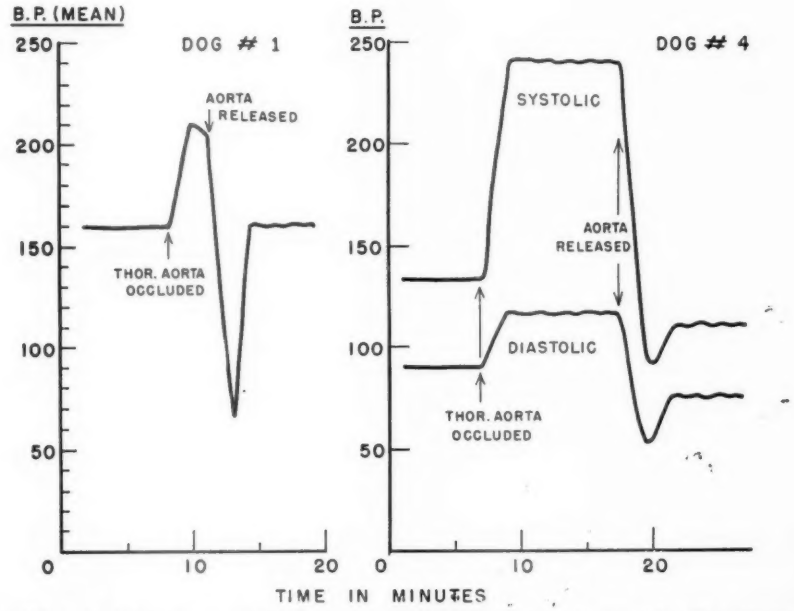

Fig. 1.—Carotid arterial pressures in Dogs 1 and 4 before, during, and after thoracic aortic occlusion.

Experiment B. Thoracic Aortic and Inferior Vena Caval Occlusion.—Next the inferior vena cava above the diaphragm and descending thoracic aorta were cross-clamped simultaneously. There was no significant change in either systolic, diastolic, or mean pressures above the level of the occlusion, the maximum rise being 10 mm. Hg and the maximum decrease being 20 mm. Hg (Fig. 2). These observations were made for periods up to 2 hours, with no change from the basic pattern just described. Although there was prominent

dilatation of the heart when the thoracic aorta alone was occluded, there was no dilatation when the inferior vena cava was simultaneously occluded and the occlusion maintained.

Experiment C. Thoracic Aortic and Inferior Vena Caval Occlusion Followed by Release of Inferior Vena Caval Occlusion.—After a period of simultaneous occlusion with maintenance of normal blood pressure in the carotid

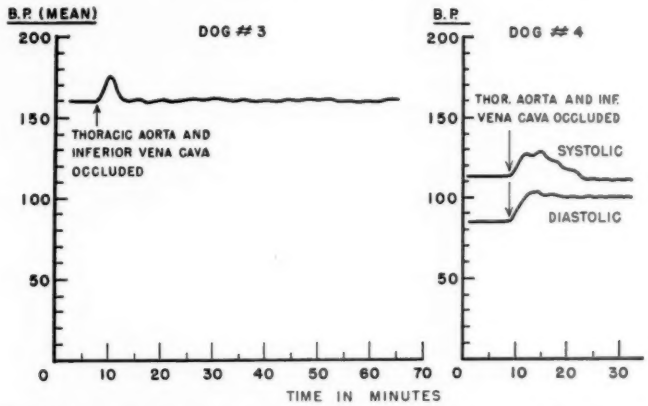

Fig. 2.—Carotid arterial pressures in Dogs 3 and 4 before and during simultaneous thoracic aortic and inferior vena caval occlusion.

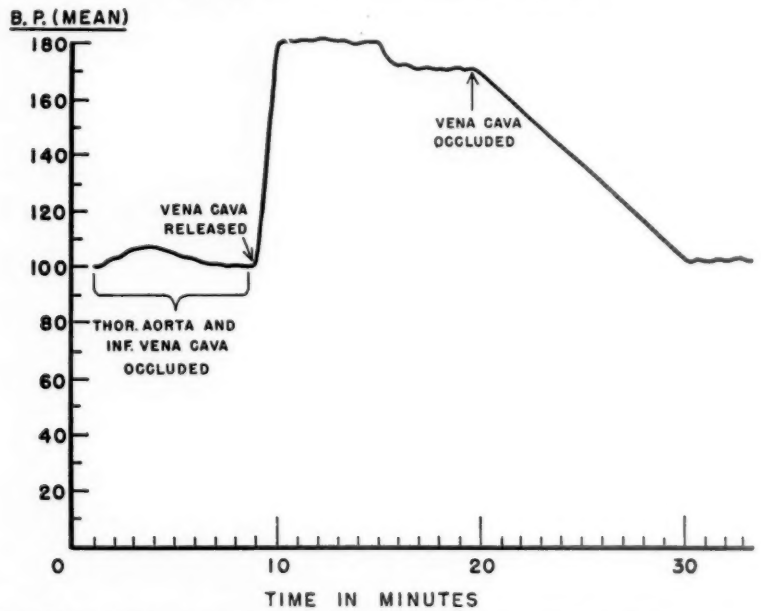

Fig. 3.—Carotid arterial pressures during simultaneous thoracic aortic and inferior vena caval occlusion. Inferior vena cava released, then reoccluded.

artery, the inferior vena caval occlusion was released while the aortic occlusion was maintained. Immediately the mean pressures in the carotid artery rose to the levels which were attained when the descending thoracic aorta only was occluded (Fig. 3). The heart immediately dilated and the heart rate decreased at times to a rate approximately one-half of the previous rate.

Experiment D. Inferior Vena Caval Occlusion Followed by Thoracic Aortic Occlusion.—When the inferior vena cava alone was occluded the mean pressures

in the carotid artery rapidly fell (Fig. 4). This was accompanied by a sudden slowing of the heart rate which gradually increased, but the pressure in the carotid artery did not rise. While maintaining caval occlusion, the descending thoracic aorta was clamped and the carotid arterial pressure rose promptly to within 20 to 30 mm. Hg below base line level.

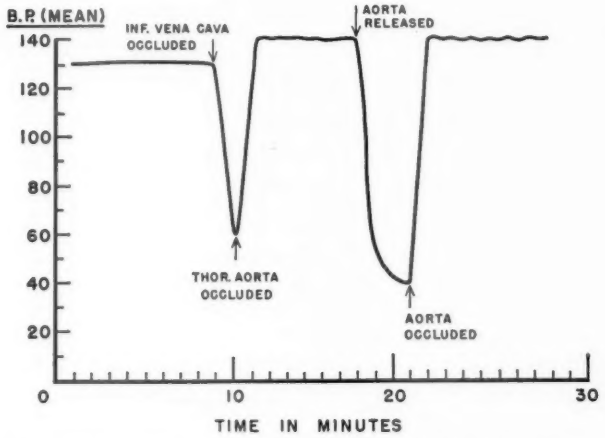

Fig. 4.—Carotid arterial pressures showing the effect of inferior vena caval occlusion. Thoracic aorta then occluded while maintaining inferior vena caval occlusion. Thoracic aortic occlusion then released and reapplied.

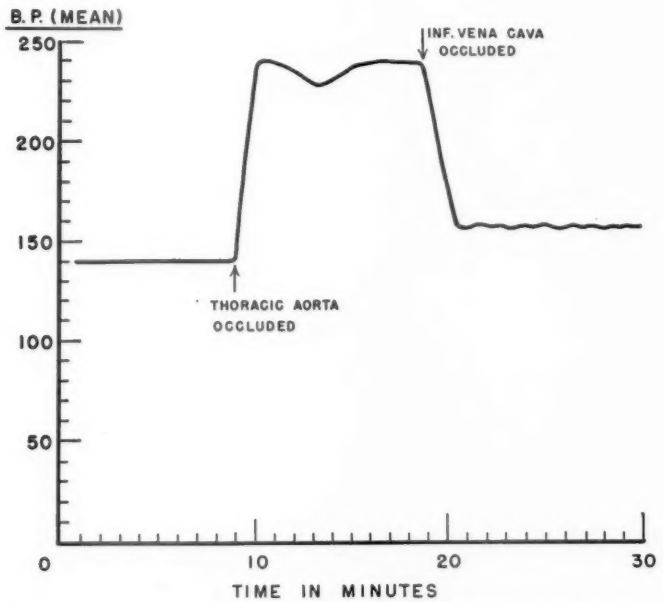

Fig. 5.—Carotid arterial pressures showing effect of thoracic aortic occlusion followed in 10 minutes by inferior vena caval occlusion.

Experiment E. Thoracic Aortic Occlusion Followed by Inferior Vena Caval Occlusion.—When the thoracic aorta was occluded as in experiment A, the carotid arterial pressure immediately rose (Fig. 5). After varying short intervals of time the inferior vena cava was occluded and the carotid arterial pressure returned within a few minutes to the previous base line level.

COMMENT

In these experiments the simultaneous occlusion of inferior vena cava above the diaphragm at the time of occlusion of the thoracic aorta prevents the carotid arterial hypertension and the cardiac dilatation that occurs when the thoracic aorta alone is occluded. Regardless of the sequence of occlusion, a relatively normal carotid arterial pressure prevails if both thoracic aorta and inferior cava are occluded. The observations of Barcroft,[1] in which he observed a rise in brachiocephalic arterial pressure upon simultaneous thoracic aortic and inferior vena caval occlusion, were all made in a period of less than one minute. In the experiments reported here there was an occasional minimal elevation of carotid arterial pressure immediately following simultaneous occlusion, but this was only 10 to 20 mm. Hg and lasted only one to two minutes. Our periods of observation following simultaneous occlusions were up to 2 hours. At this time the mean carotid pressure was usually about 10 mm. Hg less than the base line pressure prior to occlusion. If the sudden increase in peripheral resistance caused by occlusion of the thoracic aorta were compensated for by a sufficient reduction in functioning blood volume, then one might expect the pressures above the occluded area to remain approximately unchanged. Apparently this is what occurs when the inferior vena cava is occluded. Evidence for this explanation is suggested by experiment D where the inferior vena cava was occluded for several minutes prior to aortic occlusion, thus allowing for possible pooling of a volume of blood in the lower portion of the body. When the thoracic aorta is then occluded, the mean pressure in the carotid artery rises, but always to a level 20 to 30 mm. Hg below the previous mean base line. When the reverse sequence is carried out and the inferior vena caval occlusion follows several minutes after the thoracic aortic occlusion, then there is a period of 2 to 10 minutes before the carotid arterial mean pressure returns to the base line level. In this situation apparently there is a temporary pooling of a volume of blood above the occluded thoracic aorta.

Clatworthy and Varco[4] have used a small bore polyethylene shunt to prevent mechanical shock after prolonged cross-clamping of the thoracic aorta in dogs. During resection of thoracic aortic aneurysms, Stranahan and coworkers[11] have employed an external shunt as a bypass. Johnson and coworkers[8] have employed a rigid plastic prosthesis to maintain blood flow through the thoracic aorta during the period of resection for an aneurysm of the thoracic aorta. King and Shumaker[9] have devised a method of bypassing blood with the aid of a Sigmamotor pump from the superior vena cava to the femoral artery during cross-clamping of the thoracic aorta. Morris and associates[10] have provided blood flow below the site of thoracic aortic occlusion by extracorporeal circulation in which blood was shunted from left auricle to abdominal aorta. However, when the necessity for thoracic aortic occlusion is of short duration, a simpler method would seem to have advantages over the bypass shunt technique.

CLINICAL APPLICATION

Prior to the experimental observations recorded above, we had 2 consecutive clinical cases in which immediately disastrous results followed the clamping of the thoracic aorta for the insertion of a Hufnagel valve in treatment of aortic insufficiency. In one case the heart was observed to dilate and cease to beat within 90 seconds following occlusion of the thoracic aorta. Resuscitation was unsuccessful. In another case the blood pressure precipitously rose to extremely high levels above the site of aortic occlusion, with resultant cerebral damage and death of the patient 5 hours after operation despite a successfully placed and functioning Hufnagel valve. As a result of these experiences and the experimental evidence that inferior vena caval occlusion is beneficial when the thoracic aorta must be clamped, a technique for clinical application of this principle was devised.

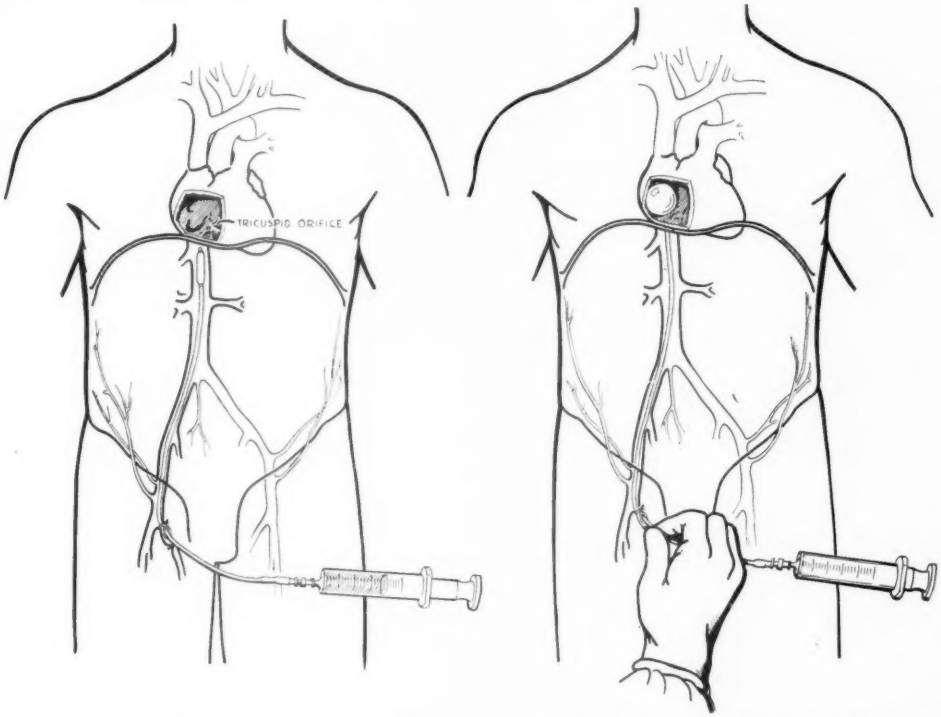

Fig. 6.—Illustration on left shows position of deflated balloon catheter in inferior vena cava at level of the diaphragm. Illustration on right shows inflated balloon in right atrium with downward traction being maintained on catheter to occlude inferior vena caval orifice.

Since the uppermost limit of the inferior vena cava is relatively inaccessible from the opened left chest, a special balloon catheter is used to occlude the inferior vena cava at its entrance to the right atrium. This catheter is introduced, under local anesthesia, via the right greater saphenous vein at its junction with the common femoral (Fig. 6). An estimated length of catheter is passed to place the tip approximately at the level of the diaphragm. A roentgenogram is obtained to check the position of the catheter tip and an adjustment is made then if necessary. Thoracotomy and exposure of the thoracic aorta is then carried out in the usual manner, with care being taken to

prevent any change in the position of the catheter during positioning of the patient on the operating table. When the point in the operation is reached at which the aorta must be occluded, the catheter is advanced 4 or 5 cm., the ballon is inflated, and downward traction is made and maintained on the catheter. With this maneuver, which will totally obstruct the inferior vena cava, the thoracic aorta is simultaneously clamped. Continuous brachial pressure recordings via an indwelling Cournand needle attached to an electromanometer are observed. After completion of aortic surgery the balloon is deflated while the thoracic aortic occlusion is gradually released.

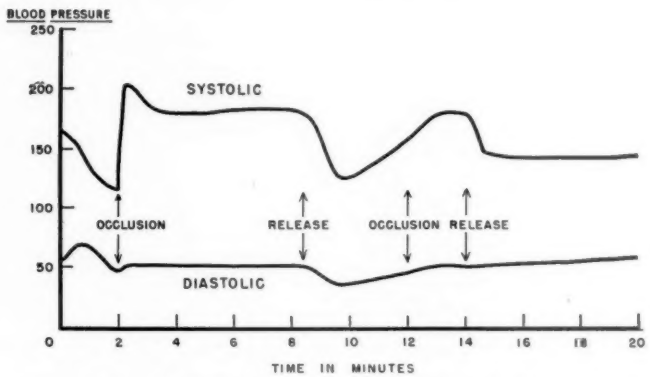

Fig. 7.—Brachial arterial pressures in Case 1.

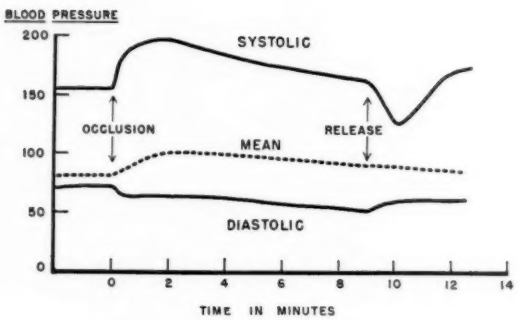

Fig. 8.

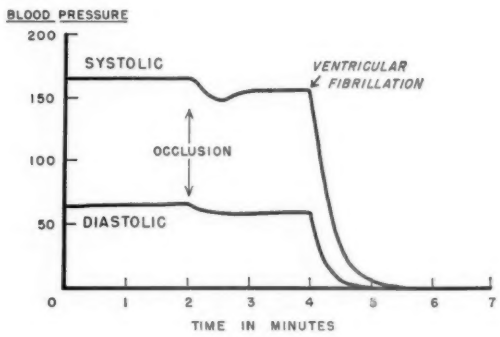

Fig. 9.

Fig. 8.—Brachial arterial pressures in Case 2.
Fig. 9.—Brachial arterial pressures in Case 3.

This technique has been used in 3 patients as an adjuvant to the insertion of a Hufnagel valve. Fig. 7 shows the brachial arterial pressure curves in Case 1, a 28-year-old white man with rheumatic aortitis and insufficiency. In this first case the thoracic aortic occlusion preceded the inferior vena caval occlusion by 30 to 45 seconds, with a resultant precipitous rise in systolic pressure above the occluded site from 116/46 to 205/50. However, with the caval occlusion maintained during the 6½-minute period of aortic occlusion, the pressures did not rise to excessive heights but fell to 180/50 during the remainder of the occlusion. A second period of simultaneous occlusion lasting 2 minutes was necessary. Again there was a slight rise in systolic pressure from 160/45 to 180/50. After release, the pressure stabilized at 145/58 and the patient had an uneventful postoperative course.

Fig. 8 illustrates the brachial arterial pressure tracing in a second patient who was a 54-year-old Negro man with syphilitic aortitis and insufficiency. Prior to occlusion of the thoracic aorta and the inferior vena cava the blood pressure was 154/70. Immediately after simultaneous occlusion the systolic pressure rose to 195/63 but did not go to extreme levels as has been our experience prior to using this method. The pressure gradually decreased so that at the end of 9 minutes of occlusion the pressure was 161/50. After release of the occlusion, the pressure stabilized at 170/60 within 2 minutes. Cardiac rhythm and rate remained relatively unchanged during the period of occlusion and the results of the procedure were quite satisfactory.

In Case 3, a 24-year-old white woman with severe syphilitic aortitis and insufficiency in whom it was planned to place a Hufnagel valve, the inferior vena cava was occluded and the thoracic aorta was occluded slowly over a one-minute period while the brachial arterial pressures were observed. By the gradual occlusion of the thoracic aorta with the inferior vena cava occluded, no appreciable change in the systolic or diastolic pressures occurred; the pre-occlusion pressures were 165/63 and one minute after occlusion 156/54 (Fig. 9). Unfortunately, ventricular fibrillation occurred 2 minutes after complete aortic occlusion and resuscitation was unsuccessful.

These cases demonstrate that a relative normotensive state can be maintained during thoracic aortic occlusion if the inferior vena cava is occluded at the level of the diaphragm. In patients with aortic insufficiency, however, it might be advantageous to allow the systolic and mean pressures to rise 10 to 20 mm. Hg above the preocclusive levels in an effort to augment coronary flow. Ideally, a rise in diastolic pressure would increase coronary flow, but no method is available to raise diastolic pressure while controlling the extremes in systolic pressure in patients with aortic insufficiency during thoracic aortic occlusion.

This procedure is relatively simple and avoids the complexity of shunts. Thus, it is ideal for short periods of thoracic aortic occlusion. Hypothermia plus this procedure will perhaps give longer protection and is currently being investigated. Simultaneous thoracic aortic and inferior vena caval occlusion in normothermic dogs prolongs spinal cord survival when compared with thoracic aortic occlusion alone.[6]

SUMMARY

Experimental study of simultaneous occlusion of the thoracic aorta and the inferior vena cava above the diaphragm has shown that this method prevents cardiac dilatation and hypertension above the occluded area which occurs when the thoracic aorta is occluded alone. A technique for clinical application is described and results in 3 patients are reported.

REFERENCES

1. Barcroft, H.: Cardiac Output and Blood Distribution, J. Physiol. **71**: 280, 1931.
2. Beattie, E. J., Adovasio, D., Keskishian, J. M., and Blades, B.: Refrigeration in Experimental Surgery of the Aorta, Surg., Gynec. & Obst. **96**: 711, 1953.
3. Blalock, A.: The Effects of Complete Occlusion of the Thoracic Aorta. An Experimental Study, J. Thoracic Surg. **2**: 69, 1932.
4. Clatworthy, H. W., and Varco, R. L.: A Small Bore Polyethylene Shunt to Prevent Mechanical Shock After Prolonged Cross-Clamping of the Thoracic Aorta, Proc. Soc. Exper. Biol. & Med. **74**: 434, 1950.

5. Erlanger, J., and Gasser, H. S.: Studies in Secondary Traumatic Shock. II. Shock Due to Mechanical Limitation of Blood Flow, Am. J. Physiol. 49: 151, 1919.
6. Gobbel, W. G., Jr., Dalton, J. B., Carlson, R. I., and Taylor, W. L.: Unpublished data.
7. Hufnagel, C. A., Harvey, W. P., Rabil, P. J., and McDermott, T. F.: Surgical Correction of Aortic Insufficiency, SURGERY 35: 673, 1954.
8. Johnson, J., Kirby, C. K., and Lehr, H. B.: A Method of Maintaining Adequate Blood Flow Through the Thoracic Aorta While Inserting an Aortic Graft to Replace an Aortic Aneurysm, SURGERY 37: 54, 1955.
9. King, H., and Shumaker, H. B., Jr.: The Use of a Mechanical By-pass During Cross-Clamping of the Aorta, J. Thoracic Surg. 34: 485, 1957.
10. Morris, G. C., Jr., Witt, R. R., Cooley, D. A., Mayer, J. M., and DeBakey, M. E.: Alterations in Renal Hemodynamics During and Following Resection of the Thoracic Aorta for Aneurysm, J. Thoracic Surg. 34: 590, 1957.
11. Stranahan, A., Alley, R. D., Sewell, W. H., and Kausel, H. W.: Aortic Arch Resection and Grafting for Aneurysm Employing an External Shunt, J. Thoracic Surg. 29: 54, 1955.

DISCUSSION

DR. DENTON A. COOLEY (Houston, Tex.).—This paper presents an ingenious solution to a rather difficult problem in surgery of the thoracic aorta. Certainly control of the pressure in the proximal segment of the aorta is important to prevent left ventricular strain and acute decompensation. This method may be useful clinically for this reason but probably would be tolerated for relatively brief periods of time in the human patient. I would like to know what happens to the pressure in the distal aortic segment during simultaneous aortic and vena caval occlusion and how this would be different from an instance of aortic occlusion without caval occulsion.

DR. HENRY SWAN (Denver, Colo.).—I would like to issue a warning about the duration of time that it is safe to occlude the inferior vena cava above the diaphragm. About 3 years ago, Dr. Owens and I found that if you occlude the vena cava between the diaphragm and heart no dog will survive 15 minutes of such occlusion. If, in addition, you clamp the descending thoracic aorta, the survival tolerance goes to about 25 to 30 minutes, but no dog survived 30 minutes of this occlusion. I noticed in these slides that these were short occlusion periods and I would like to issue warning to anyone wishing to apply these experiments that there is a time limit.

DR. H. WILLIAM SCOTT, JR. (closing).—I would like to comment on 2 other patients in whom the technique described by Dr. Gobbel has been used. Both of these had aortic insufficiency and Hufnagel valve implantations. (Slide.) This slide shows the arterial pressure tracings in one patient with aortic and caval occlusion. There was a technical delay of 20 to 30 seconds in caval occlusion after clamping the aorta and the central aortic pressure rose abruptly to a level of about 200 and then fell a bit in the next few minutes while the valve was inserted. This represented only fair control of the central pressure because of the slight delay in blocking the cava. (Slide.) In the next patient, however, very accurate control of the central aortic pressure was accomplished by occluding the inferior cava and the descending aorta simultaneously. There was no significant rise in arterial pressure, but, unfortunately, after about 2 minutes of occlusion ventricular fibrillation supervened and resuscitation was not successful. This has made us wonder if a slight increase in central aortic pressure during thoracic aortic occlusion in patients with aortic regurgitation might serve to enhance coronary flow and thus be protective.

It is our feeling that this technique should reduce the hazards of brief periods of aortic occlusion and perhaps eliminate the need for a sleight-of-hand performance in inserting a Hufnagel valve.

In answer to Dr. Swan's question, inferior caval and aortic occlusion is less apt to result in paraplegia than is aortic occlusion alone. In studies of this point, Dr. Gobbel has found that 85 per cent of dogs with both great vessels occluded for 30 minutes at normal temperatures survive without paralysis while only 10 per cent of animals fail to have paraplegia when the thoracic aorta alone is clamped for a similar period.

(Society for Vascular Surgery articles will be concluded in the February, 1958, issue of SURGERY.*)*

Book Review

CONDUCTED BY J. GARROTT ALLEN, M. D.

Surgical Technique and Principles of Operative Surgery. A. V. Partipilo. Philadelphia, 1957, Lea & Febiger, Pp. 966. $20.00.

The sixth edition of *Surgical Technique* is organized into 81 chapters intended to present the practical aspects of the subjects of general and thoracic surgery. Thirty-eight of the chapters are new in this edition, while the other chapters have been revised. Individual chapters discuss general surgical procedures, fluid therapy, blood transfusion, and the use of radioisotopes. Three well-written chapters, new in this edition, are devoted to the choice of anesthetic, its administration, and the operative and postoperative complications of anesthesia. Nine chapters describe the disturbed anatomy and physiology of congenital and acquired cardiovascular disease, together with the pertinent surgical procedures. The volume is profusely illustrated with well-labeled anatomic drawings that demonstrate pertinent structures and relationships clearly. At the ends of the chapters the authors have included questionnaires that serve as a convenient method of review and bibliographies that enable the reader to study many subjects more extensively.

While this text is, as its name implies, primarily concerned with descriptions of operative procedures, the authors have endeavored to present not only the normal anatomy and relevant embryology of the regions concerned but also the pertinent physiologic, pathologic, and clinical aspects of the subjects under discussion, together with the extent to which these considerations affect the indications for surgery and the choice of operation. Preoperative and postoperative care is discussed for each procedure and in some cases entire chapters are devoted to these subjects. The technical descriptions are presented step by step in minute detail and include most of the major general surgical procedures now in use. Each phase of the surgery is carefully illustrated by anatomic drawings that add greatly to the clarity of the presentation. In general, the techniques described are those used successfully by the authors.

Although the selection of subjects for any text is necessarily limited by space and the choice of the author, several important omissions appear in this text. It would seem appropriate to include in a text of this scope a description of the operative treatment of burns. Similarly, the extensive and thorough treatment of the surgery of the neck might include a presentation of tracheostomy procedures. The techniques of amputation are omitted. Minor procedures are accorded minor emphasis. There are a few misleading passages in the text. On page 59, the statement, "Nearly all the old blood plasma substitutes and expanders of the past fell into disuse when large numbers of patients were infected with homologous serum hepatitis," requires clarification since the transmission of homologous serum jaundice occurs through infected blood and blood products. On page 106, the first line should read, "into the sella turcica," instead of "into the sphenoid." On page 54, the word, *prothrombin,* appears where it should be *thrombin.* Typographical errors appear infrequently and are for the most part easily understood.

However, despite the criticisms, *Surgical Technique* contains a great deal of information organized and presented in a logical and systematic manner that has produced a useful reference for those interested in learning a rational surgical technique.

—Edward A. Stemmer

Calendar of Surgical Meetings

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* April 23-25, 1958, Edgewater Gulf Hotel, Edgewater Park, Miss. Secretary-Treasurer, Dr. Wm. J. Engel, 2020 East 93rd Street, Cleveland, Ohio.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN COLLEGE OF SURGEONS. *Annual Meeting of Southern California Chapter,* Jan. 17-19, 1958, El Mirador Hotel, Palm Springs, Calif. Secretary-Treasurer, Dr. Max R. Gasper, 211 Cherry Avenue, Long Beach 2, Calif.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* April 16-18, 1958, Waldorf-Astoria, New York, N. Y. Secretary, Dr. William A. Altemeier, Cincinnati General Hospital, Cincinnati, Ohio.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* April 28–May 1, 1958, Roosevelt Hotel, New Orleans, La. Deadline for submission of papers Dec. 1, 1957. Secretary, Dr. Samuel L. Raines, 188 South Bellevue Boulevard, Memphis 4, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 20-22, 1958, Columbus, Ohio. Deadline for submission of abstracts, Nov. 15, 1957. Secretary, Dr. Charles D. Branch, 1002 N. North Street, Peoria, Ill.

THE HARVEY CUSHING SOCIETY. *Annual Meeting,* April 21-23, 1958, The Mayflower, Washington, D. C. Secretary, Dr. David L. Reeves, 316 West Junipero Street, Santa Barbara, Calif.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Papers, dealing with new and unpublished work, must be submitted with abstract (not over 200 words) before October, 1957. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 3-5, 1958, Biltmore, Santa Barbara, Calif. Secretary, Dr. Carlton Mathewson, Stanford University Hospital, San Francisco, Calif.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 13-15, 1958, Boston, Mass. Deadline for submission of abstracts three months prior to meeting. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.